DEC 3 - 1931

VOLUME 48 IN TWO PARTS—PART I NUMBER 5

ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Cambridge, Mass. WARFIELD T. LONGCOPE, Baltimore

J. H. MEANS, Boston WALTER W. PALMER, New York City

W. S. THAYER, Baltimore

NOVEMBER, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $7.00

Entered as Second-Class Matter, January 22, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

CONTENTS OF PREVIOUS NUMBER

OCTOBER, 1931. NUMBER 4

The Treatment for Secondary Anemia: A Study of the Results in One Hundred and Twenty-Six Cases. Chester S. Keefer, M.D., Boston, and Chi-Shih Yang, M.D., Peiping, China.

Metabolism in Myotonia Atrophica: Report of a Case. Sergius Morgulis, Ph.D., and Alexander Young, M.D., with the Assistance of J. K. Miller and E. Jaycox, Omaha.

Tuberculous Meningitis with Syphilitic Meningitis Terminating in Recovery: A Review of the Literature. David W. Kramer, M.D., and S. E. Sheps, M.D., Philadelphia.

The Cause of Encephalopathia Gelatinosa: A Biochemical Hypothesis. William S. Keenan, M.D., Detroit.

The Elimination of Phenolsulphonephthalein by the Kidney: The Influence of Pathologic Changes in the Liver. J. P. Hauser, M.D., and G. H. Whipple, M.D., Rochester, N. Y.

Tumors of the Suprarenal Gland with Special Reference to Carcinoma of the Cortex: Report of a Case. Jacob Meyer, M.D., and Gerald Fremont, M.D., Chicago.

Tumors of the Heart and Pericardium: Pathology, Symptomatology and Report of Nine Cases. Wallace M. Yater, M.D., Washington, D. C.

Functional Aspects of Regenerated Hepatic Tissue. T. L. Althausen, M.D., San Francisco.

Normal Asymmetry and Unilateral Hypertrophy. George Halperin, M.D., Chicago.

Isolated Congenital Dextrocardia: Report of Two Cases with Unusual Electrocardiographic Findings; Anatomic, Clinical, Roentgenologic and Electrocardiographic Studies of the Cases Reported in the Literature (to be Concluded). S. S. Liebman, M.D., New York.

Book Reviews.

COPYRIGHT, 1931, BY THE AMERICAN MEDICAL ASSOCIATION

Archives of Internal Medicine

VOLUME 48 NOVEMBER, 1931—IN TWO PARTS—PART I NUMBER 5

THE CAUSATION AND PREVENTION OF CONGENITAL HEART DISEASE*

WILLIAM D. REID, M.D.

BOSTON

Congenital malformations of the heart are relatively uncommon but important in that they may seriously impair the health and longevity of the individual or cause the death of the infant at or shortly subsequent to its birth. My purpose in this article is to present evidence that congenital heart disease may be caused by some of the same factors as those that produce reduced fertility of the parents.

Embryologists employ the term "monster" to apply to fetuses and full term infants in whom congenital malformations are present. The word monster is applied whether the malformations are of the heart, nervous system or elsewhere. This explanation is given as many of the statements to be quoted were made in reference to monsters, but are considered applicable to the problem of congenital malformations of the heart.

OPINIONS AS TO THE CAUSE OF CARDIAC MALFORMATIONS

Most clinical writers express the opinion that the etiology of congenital malformations of the heart is unknown. In support of the assertion that this represents the current opinion, note the following quotation from a pamphlet [1] published by the American Heart Association in 1930. In a discussion of organic heart disease, the pamphlet reads: "The congenital type is comparatively rare and means always that a child has been born with an accidental defect, as unexplainable as a hare lip or webbed fingers."

Mall,[2] in 1917, stated that monsters are not due to germinal and hereditary causes, but are produced from normal embryos by influences that are to be sought in their environment. The primary cause is the environment of the egg, and the arrested development is associated with destruction of the tissue.

* Submitted for publication, Feb. 14, 1931.

* From the Evans Memorial and Boston University School of Medicine.

1. What Is Heart Disease? New York, American Heart Association, Inc., 1930 series, no. 5, p. 5.

2. Mall, F. P.: On the Frequency of Localized Anomalies in Human Embryos, and Infants at Birth, Am. J. Anat. **22**:1:49 (July) 1917.

Thomson,[3] in a discussion of the classification of the abnormalities found in congenital heart disease into the categories of (1) malformations and (2) intra-uterine endocarditis, objected to the latter. He wrote:

> Until recent years, many of the appearances found in congenitally malformed hearts, such as thickening and puckering of valves and adhesion of their cusps, were regarded as the result of intrauterine endocarditis; but Keith has given strong reasons for believing that this was a mistake, and that congenital malformations such as those of the heart are due generally, if not always to noninflammatory processes. When endocarditis is found in a case of congenital defect of the heart it has, therefore, probably always been secondary to the fault in development.

Thomson suggested that anything that interferes with the health of the mother during early pregnancy may favor the occurrence of cardiac malformations.

Keith[4] asserted that congenital malformations are hereditary, but that the circumstances that give rise to them are unknown. Meyer[5] wrote:

> Although we know very little about the existence of abnormal ova, the relative frequency with which anomalous forms of spermatozoa occur would alone seem to make decidedly venturesome the assumption that there is no such thing as germinal anomalies. In view of the fact that we frankly recognize the occurrence of hereditary anomalies, germinal causes certainly cannot be excluded.

Maude Abbott,[6] in her study of 850 cases of congenital heart disease, found that a history of congenital disease in the ancestry is much less common than is one of cardiac defect or other anomaly in other members of the same generation. There was a history of congenital defect in a brother or sister of the patient in 11 cases. In not a few instances the parents had both reached advanced middle life, and in some the child was the last of a series of many pregnancies.

Dr. Abbott considered the fact that mongolian idiocy occurs in the last offispring of elderly parents, apparently as an "exhaustion product" to be an extremely suggestive parallel. She wrote:

> The fact, however, advanced by Halbertsma and others, that Mongolian idiocy in twins never affects both members when these are of different sexes, i. e., are indisputably the result of a multiovular twin pregnancy (thus pointing to a disorder of the germ plasm as a cause), must, however, be harmonized with any theory of a common origin of the cardiac anomaly.

---

3. Thomson, J.: Congenital Malformations of the Heart and Large Vessels, in Oxford Medicine, New York, Oxford University Press, 1920, vol. 2, p. 375.

4. Keith, A.: Human Embryology and Morphology, ed. 4, New York, Longmans, Green and Company, 1921, p. 44.

5. Mall, F. P., and Meyer, A. W.: Studies on Abortuses: A Study of Pathologic Ova, Contrib. Embryol. C. 12, Carnegie Inst., Washington, D. C. **56**: 48, 1921.

6. Abbott, M., cited by McCrae, T., and Funk, E. H., in Osler: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 626.

Brousseau,[7] on the other hand, stated:

> Our statistics, however, do not bear out the general belief that the mongol is an exhaustion product due to the advanced age of a mother who is near the end of the child-bearing period.

In many instances the parents were young. Brousseau is of the opinion that mongolian imbecility is possibly induced by some obscure disturbance of the ductless glands.

DEVELOPMENT OF THE HEART

Embryologists divide the development of the heart into several periods. The third period, which includes[8] embryos from about 10 to 20 mm. vertex-breech measurement and extends from the fifth to the eighth week of fetal life, shows not only the completion of the subdivisions of the heart (save that the foramen between the auricles, i. e., foramen ovale, is not closed until post partum) but also the almost complete development of the valve apparatus.

In the period that follows the eighth week and continues until birth, the parts of the heart that have been already elaborated undergo[8] further modeling and are slightly altered, but any extensive transformation of the constituent parts of the heart is not seen. The same is true also with regard to the further histologic differentiation. The same embryologists[8] stated that the valve apparatus alone undergoes further elaboration in that the differentiation of the valve cusps, the chordae tendineae and the musculi papillares make further progress, and the formal differentiation of the semilunar valves increases. The walls of the heart become less membranous and more muscular. The muscular portions of the valves increase.

The chart depicts in graphic form the age and size—crown-rump length in millimeters—of the fetus. The table shows the development of the heart in relation to the age and size of the fetus. According to the authorities on embryology, whose writing I have consulted, the development of the structures of the heart is completed by the end of the eighth week of intra-uterine life.

According to a recent study,[9] the changes in circulation following birth are gradual rather than abrupt. The obliteration of the ductus

7. Brousseau, K.: Mongolianism, revised by H. G. Brainerd, Baltimore, Williams & Wilkins Company, 1928, p. 29.

8. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, vol. 2, p. 556.

9. Christie, A.: Normal Closing Time of the Foramen Ovale and the Ductus Arteriosus: An Anatomic and Statistical Study, Am. J. Dis. Child. **40**:323 (Feb.) 1930.

arteriosus is not complete until from six to eight weeks after birth, and complete anatomic closure of the foramen ovale ensues prior to twelve weeks postpartum. The portion of the aorta between the origin of the left subclavian artery and the entrance of the ductus arteriosus ("isthmic portion") which, in the fetus, is characteristically narrowed, takes two months or more to widen to the bore of the aorta below the ductus.

MONSTERS

Malformed fetuses have been produced by subjecting the embryo to certain chemicals.[10] Potassium arrests the development of the heart, and sodium produces spina bifida. Scammon [11] wrote that it has been shown that embryonic duplications of all grades and degrees may be produced in certain vertebrate embryos by changes in temperature, by

Size and Age of Fetus: Development of Heart

Crown-Rump Length,* Mm.	Age,† Days	Heart †
1.3	23	In form of two tubes preceded by cardiogenic plates
2	24	A single tube
5–7	34–37	Septum 1 in common atrium, endocardial cushions in atrioventricular canal
6–7	35.5–37	Pulmonary veins
9	40	Foramen ovale
11	42	Septum 2 in right atrium
12	43	Fusion of septum 1 and endocardial cushions
15–20	46–53	Closure of interventricular foramen
Third postnatal month		Fusion of septums 1 and 2, affecting anatomic closure of foramen ovale

* Estimated from growth curve shown in the chart.
† From Jordan, H. E., and Kindred, J. E.: A Textbook of Embryology, New York, D. Appleton & Company, 1926, p. 139.

subjection to the x-rays and ultraviolet rays, by pressure, by mechanical separation, by changes in the salt concentration and oxygen content of the surrounding medium, and by a number of other experimental procedures.

Mall [12] pointed out that monsters both in nature and when made experimentally, tend to group themselves, i. e., the malformations involve mostly a particular system of the body, as the nervous or the cardiac, in the individual fetus. He considered that grouping of monsters shows that certain tissues are influenced at crucial periods in their development, and not that given substances have specific influences on the embryo as a whole.

10. Mall, F. P.: A Study of the Causes Underlying the Origin of Human Monsters, Philadelphia, The Wistar Institute, 1908, p. 32.

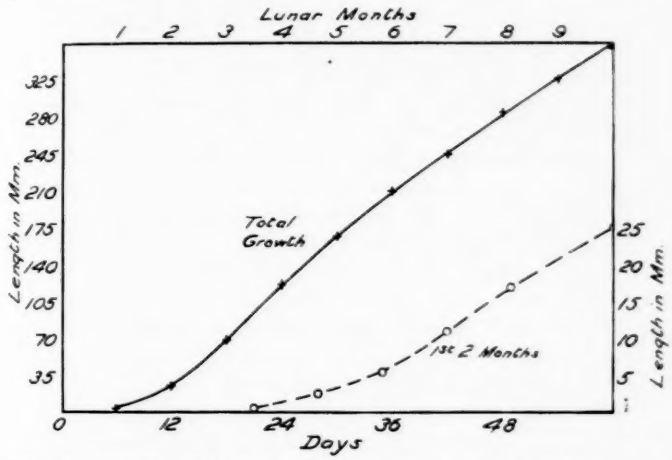
11. Scammon, R. E.: Fetal Malformations, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1925, vol. 6, p. 654.

12. Keibel and Mall: The Pathology of the Human Ovum, 1910, vol. 1, p. 240.

Mall's [12] presentation of the pathology of the human ovum contains some interesting points. He stated:

Between the fifth and sixth weeks, when the peripheral nervous system appears, the delineation of the organs becomes sharper. Here we also often find dissociation of one or more of the tissues or organs, a gorged vascular system, and frequent hydrocephalus, all probably due to an arrest of the heart action. Such embryos rapidly undergo secondary changes and within a month most of them abort, or if the chorion remains it may form the nucleus of a mole.

During the sixth week . . . the vascular system suffers very much, probably on account of the impaired nutrition on the heart. As a result of the weakened heart the cavities of the brain and body become dropsical, and the tissues of the extreme ends of the embryo dissociate and develop poorly. The precartilages and cartilages suffer least of all.



Growth curves plotted from data given by Prentiss and Arey (A Laboratory Manual and Text-Book of Embryology, ed. 2, Philadelphia, W. B. Saunders Company, 1917, p. 88). The solid line indicates the growth curve during the entire ten lunar months of pregnancy; the broken line, the growth curve during the initial two months. The crown-rump length in millimeters is indicated on the respective sides of the graph.

Seventh week . . . the extreme ends of the embryo are profoundly changed, due probably to affections of the heart of the embryo; there is much cytolysis and dissociation of the nervous system; and the face, head, and extremities are often atrophic.

Toward the eighth week there is great diminution of the number of pathological ova in my collection, as was also the case in that of His. It follows that most monsters are formed before the eighth week; those with radical changes in them are aborted. . . .

That great varieties of dropsy, as pictured by Kollmann and as frequently seen in embryos and fetuses, are due to impairment of the action of the heart is now definitely established by the enucleation experiments of Knower. It is now no

longer necessary for us to seek the mechanical obstructions which may compress the umbilical cord, such as amniotic bands, for it is now clear that the impairment of nutrition which naturally follows faulty implantation, or the various poisons which may be in a diseased uterus, can do the whole mischief.

Mall found localized anomalies to be twelve times as frequent in abortions as are monsters among fetuses at term.[5] It appears to be desirable, therefore, to present some of the available information pertaining to miscarriages.

MISCARRIAGES

In this article the term miscarriage is used to indicate all cases in which the fetus is lost before it is viable. Miscarriages, as is well known, are frequent. Meyer [5] estimated that there is 1 to every 4.54 full term pregnancies, and that but a small percentage of his series of 697 cases were due to interference by the patient. Mall [13] collected the statistics of a number of observers, and on the basis of about 100,000 cases estimated that approximately 7 per cent of all pregnancies terminate in aborted pathologic ova and about 0.6 per cent in malformed children at term. Most of the abortions that Meyer [5] classified as pathologic were young, whereas the majority of the older fetuses were normal. This same embryologist considers pathologic conditions of the chorion and decidua to be especially frequent causes for the termination of pregnancy during the early months. He grants that slips, slight falls and psychic disturbances may be the immediate but not the ultimate cause of abortions. In regard to such miscarriages, he wrote: "They remind one of the defective fruit which persists insecurely upon the tree until a sudden gust of wind showers it to the ground."

There is reason to doubt if it is good judgment to attempt to prevent a threatened miscarriage since the possibility of the birth of a monster must be considered. Whitehouse [14] mentioned (the literature contains other reports; one is also known to me) two cases in which miscarriage was staved off successfully only to result in the birth of infants with anencephalia and spina bifida, respectively.

Reynolds and Macomber [15] asserted that the great majority of miscarriages are due to imperfect conception. They found that a defective condition in either partner has been attended by miscarriages, and that after that partner has been put in good general condition subsequent pregnancies have progressed normally. These latter observers pointed out that studies of the specimens passed in human miscarriages have disclosed that in a large proportion of the cases the fetus was imperfect.

13. Mall, F. P.: A Study of the Causes Underlying the Origin of Human Monsters, J. Morphol. **19**:1, 1908.

14. Editorial, J. A. M. A. **94**:489 (Feb. 15) 1930.

15. Reynolds, E., and Macomber, D.: Fertility and Sterility in Human Marriages, Philadelphia, W. B. Saunders Company, 1924, pp. 181-198.

Reynolds and Macomber [15] also discussed failure of nidation, or imperfect implantation of the fertilized ovum in the uterine mucosa. They consider that certain local conditions such as chronic congestion, endometritis, displacements and new growths of the uterus may prevent nidation or render the attachments so imperfect that the development of the maternal portion of the decidua is hindered, with the result that the death of the fetus is caused at some period in pregnancy, and then of course, miscarriage follows.

In addition, the endocrine factor [16] must not be overlooked. It is now well known that in some cases the occurrence of repeated miscarriages seems to be related to abnormality in the function of the endocrine glands in one or both parents, and when this condition is rectified subsequent pregnancies may go on to full term.

MALE RESPONSIBILITY

Studies of the specimens passed in human miscarriage have disclosed that in a large proportion of the cases the fetus is imperfect. In their discussion on this subject, Reynolds and Macomber [15] stated:

> Most such imperfections of the fetus are the result of imperfect or otherwise abnormal segmentation in the ovum, and since segmentation is governed equally by the chromosomes derived from the male and female pronuclei, it is evident that the genetic condition of the father at the time of the formation of the efficient spermatozoon which furnishes the male pronucleus, is as important to the fetus as that of the mother at the time of the formation of the ovum, and its pronucleus.

The remarks of Meyer [5] (previously quoted) regarding the occurrence of abnormal spermatozoa and the probable bearing of germinal anomalies on the causation of monsters are recalled.

Meaker [17] found that about one third of the factors inducing infertile matings can be attributed to the male. He added that it is now well known that many of the factors that tend to prevent conception may also operate to cause miscarriage when conception does occur.

Bardeen [18] produced total monsters by subjecting the sperm of toads to roentgen radiation, before fertilization. Radiation with the roentgen rays of the eggs and sperms of certain aquatic animals and then their fertilization by normal untreated sex cells of the opposite sex, also pro-

16. Rowe, A. W.: Endocrine Studies: XXVI. The Endocrine Influence in Sterility, J. A. M. A. **95**:1219 (Oct. 23) 1930.

17. Meaker, S. F.: Constitutional Factors in the Causation of Sterility, J. A. M. A. **92**:1493 (May 4) 1929.

18. Bardeen, C. R.: Abnormal Development of Toad Ova Fertilized by Spermatozoa Exposed to the Roentgen Rays, J. Exper. Zool. **4**:1 (Feb.) 1907.

duced deformed larvae. Little and Bagg [19] reported some positive results in experiments on sheep and chicks. However, the results of these experiments do not seem to be transferable to man, for Snyder [20] stated that there are no reports of abnormal children resulting from the irradiation of nonpregnant women or of men.

It seems fair to conclude then that as yet convincing evidence is lacking of the causation of monsters by defective germ plasm in the human male; on the other hand, it appears unwarranted to exclude this factor. The roentgen rays are not the sole method nor are they nature's method of affecting the quality of sperm.

WHY SO FEW MONSTERS?

Mall,[12] whose statement that monsters with radical changes are aborted has already been cited, believed that only those that are slightly affected continue to develop until full term. Mall asserted that in order that a monster shall continue throughout pregnancy, the changes in the embryo must not be extreme enough to eliminate the heart, and the chorion must be normal enough to permit the formation of a healthy placenta, which begins to differentiate at the time (end of the second month) that monsters cease to form.

Meyer [5] pointed out that experience in the dissecting room has disclosed that pronounced malformations frequently are present internally without having become evident externally. He considers that the internal malformations must more often be the cause of the death of the embryo. Meyer asserted that cardiac anomalies, especially septal defects, and internal hydrocephalus, probably seriously affect the further development of the embryo, even if not evident externally.

It seems reasonable to believe, therefore, that a large percentage of malformed products of conception die as embryos and are aborted. The recognition of abnormal abortions is by no means simple and, unless dissected, the presence of internal malformations may readily escape notice. These factors tend to lessen the number of infants born with congenital malformations.

Parents whose fertility is of sufficient degree beget normal or abnormal children; those with insufficient fertility beget no offsprings, i. e., the mating is sterile. It is my belief that only when (1) the combined fertility of the parents is at a level between that leading to a normal offspring and that of sterility, or (2) imperfect nidation occurs, or both, then congenital malformations are likely to occur. The level of fertility

19. Little, C. C., and Bagg, H. J.: The Occurrence of Two Heritable Types of Abnormality Among the Descendants of X-Rayed Mice, Am. J. Roentgenol. **10**:975, 1923).

20. Snyder, L. H.: Roentgen Rays Induced Sterility, and the Production of Genetic Modifications, Am. J. Roentgenol. **14**:241, 1925.

is not necessarily constant, but may rise or fall. Likewise, the conditions in the uterus that predispose to imperfect implantation of the ovum and development of the chorion and decidua are not necessarily constant. Thus it is that the factors predisposing to malformation of the embryo may change sufficiently to prevent the occurrence of congenital anomalies.

The question arises, Do congenital malformations recur in the same families? They may, for without special research I personally know of four such cases. Maude Abbott [6] has been cited as having noted eleven cases in her series of congenital heart disease.

RELATION TO ENDOCRINE GLANDS

There is ample ground for considering that the ovaries, aside from the production of ovum, are among the potent regulators of the reproductive function in the female. Further, during the earlier phase of pregnancy, at least the corpus luteum has been demonstrated to exercise a highly specific and essential influence.

The experimental work performed to establish more exactly the function of the corpus luteum has been reviewed by Vincent,[21] who summarized the information as follows:

> The secretion of the corpus luteum, then, sensitizes the uterine mucosa and makes it capable of reacting to mechanical stimulation. There is a relation between the quantity of secretion on the part of the yellow body and the degree of response which can be obtained by a mechanical stimulation. The response is only obtained when sufficient secretion to sensitize the mucosa has been poured out. If the stimulus be applied when the body is just beginning to secrete, little effect may be produced. But if the application be made later, when the uterine wall has become completely sensitized, the secretion of the substance goes on for a few more days and increases the reaction. The ovum becomes attached at about the time when the greatest sensitization of the mucosa has been obtained (Loeb).

Evans [22] stated that the gonads are particularly sensitive to some disturbance in general health and also are dependent [23] on the other glands of internal secretion. He believed that trophic disturbances of the ovaries may be produced by general bodily or constitutional upsets, undernutrition, such diseases as chlorosis, tuberculosis, anemias, scarlet fever, typhoid, chronic nephritis and diabetes. Evans listed also the obese state, drugs such as morphine, and to a lesser extent alcohol, and radiations such as roentgen rays and radium, as having an unfavorable influence on the ovarian glands.

---

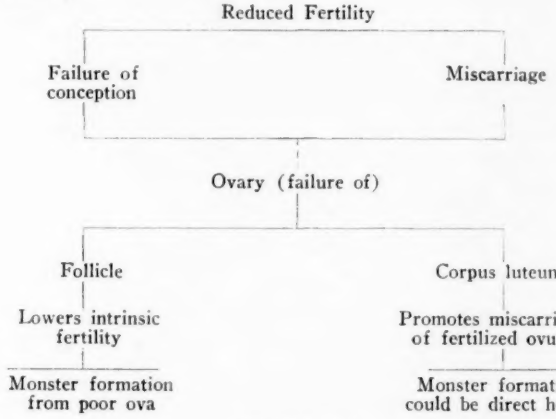
21. Vincent, S., in Barker, L. F.: Endocrinology and Metabolism, New York, D. Appleton & Company, 1922, p. 566.

22. Evans, H. E. (footnote 21, p. 595).

23. Novak, E.: Menstruation and Its Disorders, New York, D. Appleton & Company, 1921, p. 275.

It appears to be less definitely known to what extent the foregoing agents affect the corpus luteum apart from the ovary as a whole. It seems reasonable to assume, however, that they affect the reproductive function in the female, and if our idea is correct they may likewise at times be factors in the causation of abnormalities in the development of the embryo. In addition, it is probable that these same agents have a similar unfavorable influence on the spermatozoa of the male.

The following is a schema of reduced fertility and monster formation in so far as it is related to ovarian failure (suggested tentatively by A. W. Rowe).



PREVENTION

In a recent Public Health Report [24] the following statement appeared which may be assumed to be the general opinion on this subject: "Little can be done to prevent the development of congenital cases (of heart disease) beyond increasing attention to the supervision of expectant mothers." This can hardly be expected to affect the problem since the development of the heart is relatively complete by the end of the eighth week of pregnancy and Mall [12] has shown that malformation does not occur after that time, and but a few expectant mothers consult a physician until somewhat later in pregnancy. The physician must act at the beginning of the pregnancy or better before another one is begun.

Others have stated that the product of every abortion should be examined by an expert, and if any pathologic condition is noted both parents should be studied according to the methods now known [25] and in process of development by those who are studying infertility in human

24. Clark, T.: Heart Disease: A Public Health Problem, Pub. Health Rep. **44**:2463 (Oct. 11) 1929.

25. Reynolds and Macomber (footnote 15). Meaker (footnote 17).

marriages. It is my opinion that the birth of an infant with congenital malformation of the heart or elsewhere should be recognized as a strong indication for a similar examination of the parents and the correction of any abnormalities that may be detected. Further pregnancies should, ideally, be deferred until suitable examination and treatment has been completed.

It is becoming evident that constitutional factors, such as endocrinopathies, chronic intoxications, faulty diet and poor hygiene are important in the productions of infertility. The more technical examination may require special equipment and knowledge. The correction of some of the constitutional factors is certainly in the domain of the family physician and should be undertaken whether or not the examination of the reproductive organs of the parents and treatment of any abnormalities found is included.

COMMENT

No exhaustive presentation of the literature has been attempted in this article. As previously stated, many of the statements quoted are applicable to monsters as a class rather than to those in which the malformations are limited to the circulatory system. This is justifiable since it seems apparent that the factors concerning congenital heart disease and monsters are essentially the same. Mall [10] believed that the evidence indicates merely that certain tissues and organs are influenced at crucial periods in their development.

An analysis of the marital history of patients giving birth to infants with congenital malformations of the heart was begun, but soon discontinued as it was not believed to give significant information. Abortions and miscarriages are so common in patients giving birth to normal infants that the occurrence of these mishaps of pregnancy does not differentiate the parents having offspring affected by congenital malformation. This analysis did, however, disclose two instances in the total of fourteen patients in which a malformed infant occurred in two pregnancies.

It is noted that Mall [12] considered that the chorion must be normal enough to permit the formation of a healthy placenta in order that a monster shall be carried to full term and not aborted in the early part of pregnancy. Reynolds and Macomber [15] pointed to the importance of abnormal states of the uterus as causes of unsuccessful nidation of the fertilized ovum or the imperfect development of the maternal portion of the decidua. This is prone to induce a miscarriage, and the fetus, whether it is abnormal or not, is not carried to full term. Do not these statements convey an implication that the etiology of congenital malformation is more probably due to defective germ plasm, in one or both parents, rather than due to local disturbances in the uterus? In other

words, if abnormal states of the uterus prevent the formation of a normal chorion, and without the latter the monster will not be carried to full term, the chorion can be assumed to have been normal and abnormal states of the uterus not present. If the carrying of a monster to full term can, therefore, make it probable that abnormal states of the uterus were not present, then to what can the causation of the monster be attributed? One is thrown back on the other factor, i. e., defective germ plasm.

It seems best not to give too much credence to the foregoing reasoning. There may be conditions in the uterus, either primary in this organ or secondary to abnormality in function of the corpus luteum, which adversely affect the development of the embryo and of the maternal portion of the decidua and yet fall short of inducing a miscarriage. Nevertheless, if the inference is correct that a defect in the germ plasm is the more probable cause of the abnormality in the development of the fetus that survives to full term, then the occurrence of unfavorable constitutional factors in the parents assumes greater importance. They are likewise more easily diagnosed and treated by the general physician.

There is an impression that if some normal children have been born, the cause for the birth of one that is malformed cannot be due to the conditions inducing diminished fertility. Reynolds and Macomber [15] asserted that a man who is once fertile is not necessarily always fertile. Meaker stated that the level of relative fertility-sterility varies widely in different persons, and within narrower limits in the same person at different times. To consider that the degree of fertility always remains the same is far from the fact.

SUMMARY

No positive conclusions as to the causation of congenital heart disease are warranted.

The formation of congenital malformations of the heart and the formation of monsters as a class are considered to be closely associated.

Most writers consider the etiology of congenital anomalies of the heart to be unknown; some give hints as to the importance of defective germ plasma and of imperfect development of the chorion and decidua.

The human heart achieves the development of its important structures by the end of the eighth week of pregnancy. Monsters form only during the first eight weeks.

Mall found malformations to be twelve times as frequent in abortions as are monsters among fetuses at term.

The problem of abortions and miscarriages appears to be definitely associated with that of defective development of the embryo.

Most miscarriages not self-induced are inevitable.

When the malformations are radical, the embryo dies and is aborted; it is only in those cases in which the changes are slight, or of such nature that the life of the embryo is not destroyed, that the monster remains in the uterus until the end of pregnancy. This is one of the factors that explains why the birth of infants with congenital malformations is relatively rare.

Monsters sometimes are born in more than one pregnancy of the same mother.

It is suggested that the birth of an infant with malformation of the heart, or with other congenital malformation, should be considered reason for the subjection of both parents to the same sort of study as is now employed in cases of reduced fertility and the correction of any defects detected.

In the absence of a proved cause for congenital malformations and the weight of the evidence presented in this article, it seems reasonable to urge that the parents of such offspring be given the benefit of the aforementioned diagnostic study and treatment.

Dr. A. W. Rowe, Dr. S. R. Meaker, Dr. S. N. Vose and Dr. A. S. Woodman gave valuable assistance in this work.

TUBERCULOSIS IN MEDICAL AND COLLEGE STUDENTS *

H. W. HETHERINGTON, M.D.

F. MAURICE McPHEDRAN, M.D.

H. R. M. LANDIS, M.D.

AND

EUGENE L. OPIE, M.D.

PHILADELPHIA

The occurrence of pulmonary tuberculosis in one or more medical students in each successive class has attracted attention in many medical schools of this country, but since early adult life is the period at which the disease most frequently has its onset it is difficult to determine if infection is more common in medical students than in young men of the same age following other occupations.

In the Harvard Medical School alumni bulletin, Steidl [1] commented on the frequency with which medical students, young physicians and nurses are found among the patients of sanatoriums for tuberculosis, and in the same number of this publication an editorial states that the toll of tuberculosis among students of the Harvard Medical School has been appalling. In the class of 1924, 10 men, or nearly 10 per cent of the class, became ill from tuberculosis during their course in the medical school or during their subsequent hospital work. Nevertheless, Fitz [2] has found little evidence of tuberculosis among 417 medical students of Harvard Medical School to whom he gave roentgenologic examinations.

The present study to determine the frequency of tuberculous infection in medical students was undertaken because a considerable number of students of the Medical School of the University of Pennsylvania, either during their medical course or in the subsequent two years as hospital interns, have been compelled by tuberculosis to interrupt their work. An intimate knowledge of the frequency and character of the infection was regarded as the first step in its prevention.

---

* Submitted for publication, March 5, 1931.

* From the Henry Phipps Institute, University of Pennsylvania.

* Aided by a grant from the Metropolitan Life Insurance Company of New York.

1. Steidl, J.: Bull. Harvard M. Alumni A. **5**:10, 1930.

2. Fitz, R.: Bull. Harvard M. Alumni A. **5**:10, 1930.

This study extends to an older group observations that have been made at the Henry Phipps Institute on the school children of Philadelphia.[3]

The examination of high school boys between the ages of 14 and 20 years revealed in a considerable number of instances pulmonary tuberculosis of the adult type, varying in extent as defined by roentgenograms, from inconspicuous shadows appearing only below the lower margin of the second rib to advanced infiltration extending downward far below the level of the clavicle, accompanied sometimes by râles and other physical signs. In some pupils the lesions advanced until health was seriously impaired, and tubercle bacilli appeared in the sputum. The present study gave the opportunity of determining the

TABLE 1.—*Results of the Tuberculin Test in College and Medical Students*

		Reacting to Tuberculin							
		0.01 Mg.		0.1 Mg.		1 Mg.		Total	
Year	Number Tested	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
First year college	64	35	54.7	14	21.9	5	7.8	54	84.4
Second year college	68	37	54.4	6	8.8	12	17.6	55	80.9
Third year college	67	47	70.1	9	13.4	6	8.9	62	92.5
Fourth year college	37	21	56.7	4	10.8	6	16.2	31	83.8
Total	236	140	59.3	33	14.0	29	12.3	202	85.6
First year medical	99	51	51.5	25	25.2	8	8.1	84	84.8
Second year medical	103	64	62.1	21	20.4	12	11.6	97	94.2
Third year medical	126	94	74.6	17	13.5	10	7.9	121	96.0
Fourth year medical	111	99	89.2	10	9.0	0	...	109	98.2
Total	439	308	70.2	73	16.6	30	6.8	411	93.6

frequency of similar lesions in young men, in great part from 17 to 27 years of age, who were attending college or medical school and who were presumably, with few exceptions, in good health.

The weight and height of all students were recorded, and each student entered on a personal history form the symptoms of any respiratory disease with which he had suffered, the occurrence of tuberculosis in his family and any other exposure to the disease. All students were given an intracutaneous tuberculin test and a roentgenologic examination of the chest, and those in whom tuberculous infiltration was recognized received physical examination. Roentgenologic examination consisted in postero-anterior stereoscopic films of the chest. Of those who received tuberculin tests, all save 1 medical student underwent roentgenologic examination. On the other hand, 43 college students and 14 medical students underwent roentgenologic examination but did not report for the tuberculin test.

3. Opie, E. L.; Landis, H. R. M.; McPhedran, F. M., and Hetherington, H. W.: Am. Rev. Tuberc. **20**:413 and 421, 1929.

The results of the tuberculin tests, with the students grouped in classes, are shown in table 1.

Among premedical college students, the percentage of those who reacted varied from 80.9 to 92.5. There was no continuous increase from class to class, and it is probable that the variation is in part explained by the small number of students in each class, namely, from 37 to 68. The average percentage of reactions for all premedical students was 85.6. Of the first year medical students, 84.8 per cent reacted to 1 mg. of tuberculin or less. This figure is approximately the same as that for premedical students, but in the second and third

TABLE 2.—*Results of Roentgenologic Examinations of College and Medical Students*

Year and Course	Number Given Roentgenologic Examination	Number with no Apparent Tuberculous Pulmonary Lesion	Number with Pulmonary Nodule	Number with Tuberculosis of Tracheobronchial Lymph Nodes	Number with Nonapical Latent Tuberculous Pulmonary Infiltration	Number with Latent Apical Tuberculosis	Number with Manifest Pulmonary Tuberculosis	Average Age of Those Examined
First year college...	78	62	8	6	0	1	1	17.8
Second year college.	79	60	5	10	1	3	0	19.1
Third year college..	81	68	2	8	0	3	0	20.1
Fourth year college	41	34	1	4	0	2	0	20.9
Total.....	279	224	16	28	1	9	1	
First year medical..	98	71	6	17 (1)	0	3	1	22.1
Second year medical	103	77	5	9 (4)	0	12	0	23.4
Third year medical..	129	89	5	16 (2)	1	14	4	24.2
Fourth year medical	122	75	5	16 (7)	1	16	9	24.3
Total.....	452	312	21	58*	2†	45‡	14§	

* Tuberculosis of the tracheobronchial lymph nodes accompanied by pulmonary infiltration, latent manifest or apical tuberculosis is indicated in brackets, and, as it is listed in the corresponding columns, it is not included in the total.

† In one instance, pulmonary infiltration was accompanied by a recognizable lesion of the tracheobronchial lymph nodes.

‡ In ten instances, latent apical tuberculosis was accompanied by recognizable lesions of the tracheobronchial lymph nodes.

§ In three instances, manifest tuberculosis was accompanied by recognizable lesions of the tracheobronchial lymph nodes.

years of the medical course the percentage reacting was higher, and in the fourth year it reached 98.2. This indicates an almost continuous increase in the frequency of infection throughout the medical course and corresponds with the increasing number of tuberculous infiltrations discovered by roentgenologic examination.

The results of the roentgenologic examination of 731 students arranged in classes are shown in table 2. When this examination revealed infiltration of the lung substance, the student received physical examination. Students with tuberculous infiltration of the lungs fall into two groups: (1) those with roentgenologically demonstrable infiltrations but with neither symptoms nor physical signs referable to

the lesion; (2) those with either symptoms or physical signs or both referable to the infiltration.

The significant symptoms were cough, hemoptysis, fever and loss of weight; the significant physical signs were râles, impaired resonance and restricted movement over the site of the lesion. When there were symptoms or physical signs referable to the lesion, the disease was regarded as manifest.

The lesions designated as pulmonary nodules and tuberculosis of the tracheobronchial lymph nodes are in all instances calcified foci representing the remains of tuberculous infection with few, if any, exceptions acquired in childhood. They are distinguished by their greater opacity and sharply defined outlines from the diffuse lesions of the lungs that are designated in the table as infiltrations.

Calcified nodules of the lungs or the adjacent lymph nodes without other demonstrable tuberculous lesion were found in 44 of 279 college students, or 15.8 per cent, and in 79 of 452 medical students, or 17.5 per cent. In ten of forty-five instances of latent apical tuberculosis in medical students and in three of fourteen instances of manifest pulmonary tuberculosis in the same group, there was associated tuberculosis of the tracheobronchial lymph nodes.

Two college students with calcified nodules in the lungs and 1 with similar lesions in the lymph nodes failed to react to tuberculin. In 5 medical students there were calcified lesions of the lymph nodes and in 1 a pulmonary nodule, but no reaction to tuberculin. In these instances, the lesions by analogy with animal experiments had presumably undergone complete healing.

Of the college students, 1 had manifest tuberculosis (fig. 1, col. I-1), 9 had apical tuberculosis without physical signs (fig. 1) and 1 had a nonapical tuberculous infiltration without physical signs. Thus of the 279 students, 11, or 3.9 per cent, had roentgenologically demonstrable tuberculous infiltrations of the lung. The number of students in each year is small, and there is apparently no significant difference in the incidence in the four college years.

On the other hand, 14 medical students had manifest pulmonary tuberculosis (figs. 2 to 7), 45 had apical tuberculosis without physical signs, and 2 had nonapical tuberculous infiltration without physical signs (figs. 2 to 7). Of the 452 medical students, 61, or 13.5 per cent, had roentgenologically demonstrable tuberculous infiltrations in the lungs. Moreover, there is a continuous increase in the incidence of lesions in successive classes of the medical school. In the first year, 4 of 98, in the second, 12 of 103, in the third, 19 of 129, and in the fourth, 26 of 122 had pulmonary infiltrations, percentages of 4.1, 11.6, 14.7 and 21.3, respectively. One instance of manifest tuberculosis occurred in the first and second year classes, four in the third year class and nine in the fourth year.

In the diagrams that accompany the case histories, we have attempted to depict the anatomic extent and in some degree the density of each infiltration. Table 3 shows the anatomic extent of the infiltrations. The clavicle has been chosen as a dividing line because it is convenient. Roentgenograms were taken so that the shadow of the clavicle was on a level with the shadow of the fourth rib posteriorly. Infiltrations confined to the apex of the lung above the clavicle are considered less dangerous than those extending below it, chiefly because they are less extensive. Serial observations show that, in early adult life particularly, infiltrations above the clavicle often progress below it within a period measured in months.

TABLE 3.—*Analysis of Apical Lesions*

Year and Course	Number Given Roentgenologic Examination	Suspected Apical Infiltration		Supraclavicular Apical Infiltration		Unilateral Apical Infiltration Extending Below the Clavicle	Bilateral Apical Infiltration Extending Below the Clavicle on One Side
		Unilateral	Bilateral	Unilateral	Bilateral		
First year college	78	2	1	1	0	1	0
Second year college	79	2	0	2	1	0	0
Third year college	81	2	0	1	2	0	0
Fourth year college	41	2	0	2	0	0	0
Total	279	8	1	6	3	1	0
First year medical	98	7	2	1	2	0	1
Second year medical	103	4	1	3	9	0	0
Third year medical	129	7	1	6	6	4	2
Fourth year medical	122	9	0	5	7	8	5*
Total	452	27	4	15	24	12	8

* In one instance, bilateral infiltration extended below the clavicle on both sides.

In nine instances in college students and in thirty-one instances in medical students, shadows of doubtful significance were seen at the apexes. These were not definitely due to infiltration extending into the lung from the apical pleura. Nevertheless, we believe that the students in whose films these anomalous shadows occur should be kept under observation. It is noteworthy that the frequency of these suspected lesions is considerably greater in medical than in premedical students.

Approximately 3 per cent of the college students had infiltration of the apex of the lungs limited to the area above the clavicle, whereas 8.6 per cent of the medical students had similar lesions. These lesions increased from 3 per cent among the first year medical students to approximately 10 per cent in those of the fourth year.

One college student had an apical infiltration extending below the clavicle. One student in the first two years of the medical course and 19 in the last two years had similar lesions. Not only was the incidence

of apical infiltrations higher among the medical students approaching graduation, but many of the infiltrations were more extensive, and, as shown in table 2, physical signs or symptoms were found thirteen times.

The factors that determine whether or not an infiltration will be latent or manifest are obscure. While one will cause definite physical signs, another just as extensive and from a roentgenologic point of view presenting an equally soft and flocculent appearance may be silent (McPhedran [4]).

One of the 15 students with manifest tuberculosis had had tubercle bacilli in his sputum eighteen months earlier, and another had had hemoptysis before the survey was made. Two others had apical râles. The rest had impaired resonance and restricted movement over the site of the lesion, in some instances with slight elevation of temperature or cough. Although pulmonary tuberculosis with râles probably represents a further stage of the disease than manifest pulmonary tuberculosis without râles, and this in turn a further stage than latent apical tuberculosis, the potentialities of all, namely, the development of progressive tuberculosis under unfavorable circumstances, are the same.

Students in whom pulmonary tuberculosis was recognized were informed concerning the character of their lesions and were given advice directed to prevent its further advance. The recommendation made to each student was determined by the anatomic extent and appearance of the infiltration in the roentgenograms, the results of physical examination, the reaction to tuberculin and the age of the patient. These recommendations were regarded as tentative because as yet there is available little information concerning the prognostic significance of tuberculous lesions discovered in those who are presumably in good health and are not known to have been in contact with persons with tuberculosis.

Those who failed to react to tuberculin were regarded as free from progressive tuberculous infection. With complete healing of the lesion, the reaction to tuberculin may disappear.

Calcified lesions of the lungs and lymph nodes were not regarded as significant unless there was an intense reaction to tuberculin. Students with an active reaction to tuberculin and recognizable lesions of the lymph nodes were advised to return for roentgenologic examination at intervals of one year.

Students with suspected or scant latent apical tuberculosis were advised to return for roentgenologic examination at intervals of six months. If the reaction to tuberculin was intense, the student was placed in the following group:

4. McPhedran, F. M.: Am. Rev. Tuberc. **20**:532, 1929.

Those with conspicuous infiltration of one or both apexes but with no symptoms or physical signs indicative of tuberculosis were advised to remain under continued medical supervision and to plan their lives to secure retrogression of the disease. They were directed to avoid physical and mental fatigue, to rest ten or more hours in bed each night, not to take part in athletic sports, to restrict muscular exercise and to give special attention to their diet. They were requested to return for roentgenologic and physical examination at intervals of three months, or within a shorter time if there were any symptoms suggestive of pulmonary disease.

Students with advanced pulmonary tuberculosis revealed by roentgenologic examination and accompanied by symptoms or physical signs referable to the disease were advised to discontinue medical work for

TABLE 4.—*Recommendations*

Year and Course	Number with no Evidence of Infection	Number with Nothing Significant Found	Number Recommended for				Number Given Roentgenologic Examination
			Annual Observation	Semi-Annual Observation	Supervision	Sanatorium Treatment	
First year college	4	67	4	2	0	1	78
Second year college	10	54	8	5	2	0	79
Third year college	3	68	6	3	1	0	81
Fourth year college	4	30	5	2	0	0	41
Total	21	219	23	12	3	1	279
First year medical	10	63	15	9	0	1	98
Second year medical	3	75	11	5	9	0	103
Third year medical	6	87	16	9	7	4	129
Fourth year medical	1	77	14	8	17	5	122
Total	20	302	56	31	33	10	452

a time and to submit themselves to treatment in a sanatorium or its equivalent. This advice accords with that customarily given to other patients in whom pulmonary tuberculosis has been found.

The recommendations given to medical students are classified in the four groups just described and are shown in table 4 because they represent the estimated severity of the lesions that were discovered.

It is interesting to compare boys in the high schools of Philadelphia with college students of the University of Pennsylvania. During a survey made to determine the prevalence of tuberculosis in school children of Philadelphia, 1,319 boys attending three high schools were given tuberculin tests, and 1,012 received roentgenologic examination. In tables 5 and 6, these examinations are compared with those made on college and on medical students, all of whom are arranged by age.

When attention is limited to the ages in which the number of students is 50 or more, an almost continuous increase in the incidence of the reaction to tuberculin is found to correspond with increase of

age, the percentage increasing from 77.4 in high school boys 15 years old to 97.2 in medical students 25 years old.

When recognition of tuberculosis at the apex of the lung, including both latent and manifest lesions, is used as a measure of the severity

TABLE 5.—*Results of the Tuberculin Test at Different Ages*

	High School Students			College Students			Medical Students		
Age	Number Tested with Tuberculin	Number Positive to 1 Mg.	Percentage	Number Tested with Tuberculin	Number Positive to 1 Mg.	Percentage	Number Tested with Tuberculin	Number Positive to 1 Mg.	Percentage
15	328	254	77.4	2	2	....	..	..	....
16	380	302	79.4	11	11	....	..	..	....
17	231	180	77.9	17	14	....	..	..	....
18	108	93	86.1	56	47	83.9	..	..	....
19	41	33	....	51	42	82.3	..	..	....
20	9	8	....	38	31	....	10	7	....
21	...	...	....	38	35	....	41	37	....
22	...	...	....	8	5	....	81	75	92.6
23	...	...	....	5	5	....	79	75	94.9
24	...	...	....	3	3	....	80	76	95.0
25	...	...	....	5	5	....	72	70	97.2
26	...	...	....	0	0	....	39	36	....
27	...	...	....	1	1	....	14	14	....
28	...	...	....	0	0	....	13	11	....
29	...	...	....	0	0	....	4	4	....
30	...	...	....	1	1	....	6	6	....

TABLE 6.—*Results of Roentgenologic Examination at Different Ages*

	High School Boys					College Students			Medical Students		
Age	Number Tested with Tuberculin	Number Reacting to Tuberculin	Number Given Roentgenologic Examination	Number with Apical Tuberculosis	Percentage with Apical Tuberculosis	Number Given Roentgenologic Examination	Number with Apical Tuberculosis	Percentage with Apical Tuberculosis	Number Given Roentgenologic Examination	Number with Apical Tuberculosis	Percentage with Apical Tuberculosis
12	12	9	9	0	...	..	..	...	..	..	...
13	54	37	37	1	1.8	..	..	...	..	..	...
14	156	110	111	1	0.6	..	..	...	..	..	...
15	328	254	249	2	0.6	2	0	...	..	..	...
16	380	302	294	7	1.8	13	0	...	..	..	...
17	231	180	179	1	0.4	20	1	5.0	..	..	...
18	108	93	92	0	0.0	65	2	3.1	..	..	...
19	41	33	33	1	2.4	66	1	1.5	..	..	...
20	9	8	8	0	...	44	2	4.5	10	0	...
21	...	...	...	..	...	45	3	6.7	41	2	4.9
22	...	...	...	..	...	9	0	...	83	6	7.2
23	...	...	...	..	...	5	1	...	78	11	14.1
24	...	...	...	..	...	3	0	...	87	14	16.1
25	...	...	...	..	...	5	0	...	75	11	14.6
26	...	...	...	..	...	0	0	...	33	10	30.3
27	...	...	...	..	...	1	0	...	14	1	...
28	...	...	...	..	...	0	0	...	19	2	...
29	...	...	...	..	...	0	0	...	5	0	...
30	...	...	...	..	...	1	0	...	4	0	...
30+	...	...	...	..	...	..	..	...	3	2	...

of infection (table 6), the incidence of these lesions is found to be 1.3 per cent in high school boys whose ages vary approximately from 12 to 19 years, 3.6 per cent in college students in great part between the ages of 17 and 21 years, and 13 per cent in medical students chiefly between the ages of 21 and 26 years.

SUMMARY

Examinations to discover the frequency of tuberculous infection were made of 279 premedical college students and of 452 medical students and were compared with similar examinations of boys attending high school.

Tuberculous infection indicated by the tuberculin test increased with age, occurring in 77.8 per cent of the high school boys, in great part between the ages of 15 and 18 years, in 85.6 per cent of the premedical college students, largely between the ages of 16 and 21 years, and in 93.6 per cent of the medical students, largely between the ages of 21 and 26 years.

The frequency of recognizable calcified nodules in the lungs and lymph nodes did not differ notably in high school boys, in premedical college students and in medical students.

Tuberculous infiltrations at the apex of the lungs were somewhat more frequent in premedical students than in high school boys and had not increased notably in students of the first year of medicine (4.1 per cent). In medical students they increased rapidly from year to year, being 11.6 per cent in second year students, 14 per cent in third year students and 20.5 per cent in fourth year students. Moreover, the frequency of advanced lesions increased at the same time, 13 students in the fourth year having lesions extending from the apex below the clavicle.

Tuberculous infiltration of the apex of the lungs accompanied by symptoms or physical signs, that is, manifest pulmonary tuberculosis, occurred once among the premedical students examined, once during the first two years of medicine, four times in the third year class in medicine and nine times in the fourth year class.

An increasing frequency of grave infection during adolescence and early adult life is evident, but there are available no comparable data concerning the occurrence of tuberculosis in young men pursuing other occupations and presumably in good health. Nevertheless, the high incidence of apical lesions in these medical students, increasing rapidly from the ages of 21 to 26, indicates that they were peculiarly subject to advanced tuberculous infection.

COLLEGE STUDENTS

FIRST YEAR

Col. I-1.—*Pulmonary Tuberculosis.*—The subject was an American Jew, aged 17. The weight was not reported. A tuberculin test was not made.

Examination.—Roentgenologic examination showed a moderately dense, soft infiltration at the apex of the left lung, extending as low as the sixth rib. Physical examination revealed limited movement over the left apex and medium moist râles above the clavicle anteriorly. There were no symptoms. Contact with tuberculosis was not recorded.

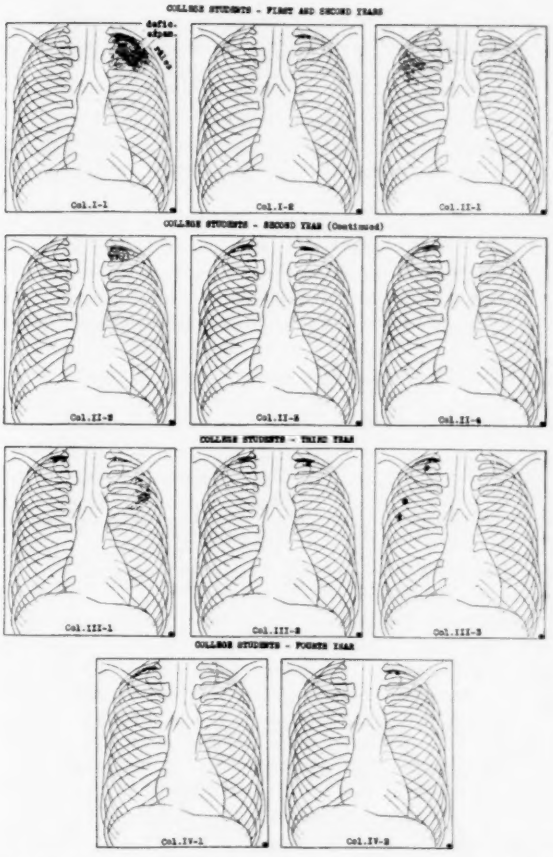


Fig. 1.—This and the succeeding diagrams show the position and extent of the lesions recognized in roentgenologic films. All instances of pulmonary infiltration of tuberculous origin are shown, and symptoms and physical signs are noted.

In the data presented, the tuberculin reaction is indicated by plus signs before a figure indicating the quantity of tuberculin injected, and the weight of each student at the time of examination is indicated as a percentage of the normal weight for height and age.

When not otherwise stated, the levels of the ribs and interspaces mentioned in the descriptions are at the posterior aspect of the thorax.

Diagnosis.—The diagnosis was pulmonary tuberculosis.

Recommendation.—Treatment in a sanatorium was advised.

Col. I-2.—*Latent Apical Tuberculosis.*—The subject was an American, aged 20. The weight was not recorded. A tuberculin test was not made.

Examination.—Roentgenologic examination showed a sharply defined salient at the apex of the left lung in the second interspace. There were no physical signs. Symptoms and contact with tuberculosis were not recorded.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Semi-annual observation was advised.

SECOND YEAR

Col. II.1.—*Latent Tuberculous Infiltration of the Lung.*—The subject was an American Jew, aged 18. The weight was 97 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed a somewhat scanty, soft infiltration in the right lung below the clavicle at the anterior levels of the first and second interspaces. Physical examination was not made. There were no symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—A diagnosis of latent tuberculous infiltration of the lung was made.

Recommendation.—Supervision was recommended.

Col. II-2.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 18. The weight was 103 per cent. The tuberculin reaction was +++ to 0.01 mg.

Examination.—Roentgenologic examination showed a somewhat scanty, soft infiltration at the apex of the left lung in the second and third interspaces. There were no physical signs or symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was advised.

Col. II-3.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 19. The weight was 83 per cent. The tuberculin reaction was + to 1 mg.

Examination.—Roengenologic examination showed: In the right lung, there was thickening of the apical pleura with salients projecting into the lung at the second interspace. In the left lung, there was a small area of scanty infiltration at the apex in the second interspace. Physical examination was not made. There were no symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was advised.

Col. II-4.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 18. The weight was 100 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed a small area of scanty infiltration at the apex in the second interspace of the right lung. There were no physical signs. Symptoms and contact with tuberculosis were not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Annual observation was advised.

THIRD YEAR

Col. III-1.—*Latent Apical Tuberculosis.*—The subject was an American, aged 21. The weight was 97 per cent. A tuberculin test was not made.

Examination.—Roentgenologic examination showed: In the right lung, there were thickening of the apical pleura and a small area of scanty infiltration in the second interspace. In the left lung, there were thickening of the apical pleura and also a strandlike infiltration chiefly in the second interspace anteriorly; the latter probably represented a long-standing lesion, possibly of childhood type. Physical examination was not made. There were no symptoms. There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis and tuberculous infiltration of the lungs was made.

Recommendation.—Semi-annual observation was recommended.

Col. III-2.—*Latent Apical Tuberculosis.*—The subject was an American, aged 21. The weight was not recorded. The tuberculin reaction was + to 1 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a scanty infiltration at the apex in the second interspace. In the left lung, there was thickening of the apical pleura with salients at the second insterspace. There were no physical signs or symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation—Supervision was advised.

Col. III-3.—*Latent Apical Tuberculosis.*—The subject was an American, aged 23. The weight was 98 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed thickening of the apical pleura of the right lung with sharply defined salients extending into the parenchyma at the second interspace, and nodules at the third rib and the fifth and sixth interspaces. Physical examination was not made. The symptoms and contact with tuberculosis were not reported.

Diagnosis.—The diagnosis was latent apical tuberculosis and peripheral calcified pulmonary nodules.

Recommendation.—Semi-annual observation was advised.

FOURTH YEAR

Col. IV-1.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 20. The weight was 108 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination revealed thickening of the apical pleura on the right side with salients projecting into the lung field in the second interspace. There were no physical signs or symptoms. Contact with tuberculosis was not reported.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was recommended.

Col. IV-2.—*Latent Apical Tuberculosis.*—The subject was an American, aged 21. The weight was 92 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed a small area of scanty infiltration at the apex of the left lung in the second interspace. Physical examination was not made. The symptoms and contact with tuberculosis were not reported.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was recommended.

MEDICAL STUDENTS

FIRST YEAR

MED. I-1.—*Pulmonary Tuberculosis.*—The subject was an American Jew, aged 21. The weight was 105 per cent. The tuberculin reaction was + to 0.01 mg.

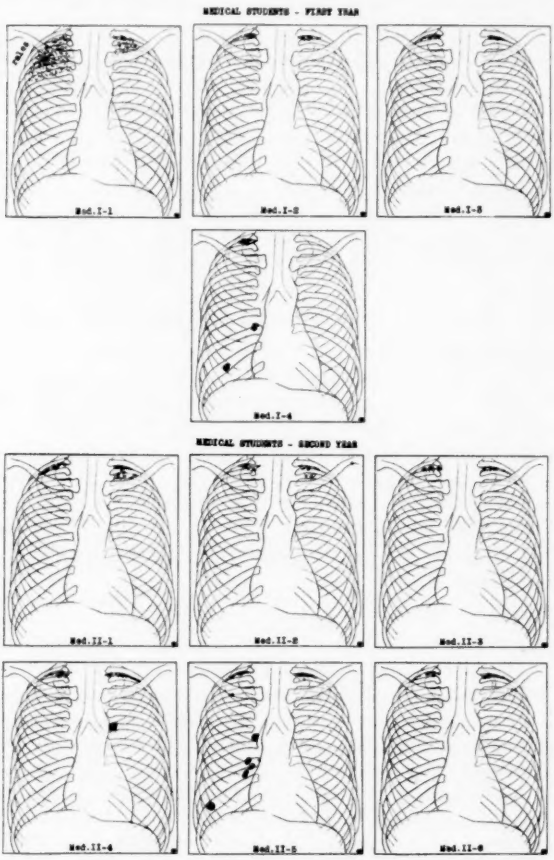


Figure 2.

Examination.—Roentgenologic examination showed: In the right lung, there was a moderately dense infiltration consisting mainly of discrete spots extending as low as the sixth rib. In the left lung, there was a similar infiltration above the clavicle. Physical examination revealed fine and medium moist râles after cough at the apex of the right lung, anteriorly and posteriorly, varying in number but constantly present. Similar râles at the apex of the left lung were inconstant. There were no symptoms. The patient had had no known contact with tuberculosis.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Treatment in a sanatorium was advised.

MED. I-2.—*Latent Apical Tuberculosis.*—The subject was an American, aged 21. The weight was 86 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was thickening of the apical pleura with infiltration in the second interspace. In the left lung, there was a similar thickening of the apical pleura. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was recommended.

MED. I-3.—*Latent Apical Tuberculosis.*—The subject was an American, aged 22. The weight was 85 per cent. The tuberculin reaction was + to 0.1 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a small area of infiltration at the apex in the second interspace. In the left lung, there was a small area of similar infiltration. Physical examination was not made. The symptoms were not recorded. The patient had had no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Annual observation was advised.

MED. I-4.—*Latent Apical Tuberculosis.*—The subject was an American, aged 23. The weight was 99 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed in the right lung a small area of infiltration at the apex in the second interspace and a calcified area at the hilus with a calcified nodule in the lung field. Physical examination was not made. The symptoms and contact with tuberculosis were not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes with a peripheral calcified nodule.

Recommendation.—Semi-annual observation was recommended.

SECOND YEAR

MED. II-1.—*Latent Apical Tuberculosis.*—The subject was an American, aged 22. The weight was 100 per cent. The tuberculin reaction was + to 0.1 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was thickening of the apical pleura with salients projecting into the lung field in the second interspace. In the left lung, there was a similar condition at the apex with infiltration in the second and third interspaces. There were no physical signs or symptoms There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was advised.

MED. II-2.—*Latent Apical Tuberculosis.*—The subject was an Englishman aged 24. The weight was 93 per cent. The tuberculin reaction was + to 1 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a scanty infiltration at the apex in the second interspace. In the left lung, there was a similar infiltration in the second and third interspaces. There were no symptoms or physical signs. There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was advised.

MED. II-3.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24. The weight was 89 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a soft infiltration at the apex in the second interspace and behind the third rib. In the left lung, there was a thickening of the apical pleura with salients

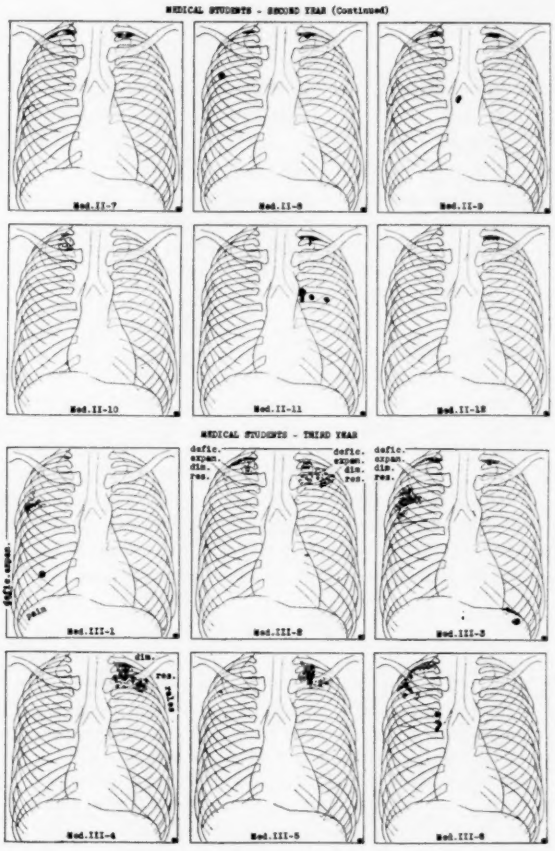


Figure 3.

projecting into the lung in the second interspace. Physical examination was not made. The symptomatology and contact with tuberculosis were not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was recommended.

MED. II-4.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 84 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was thickening of the apical pleura with infiltration in the second interspace. In the left lung, there was a thickening of the apical pleura with salients projecting into the lung in the second interspace and a calcified area at the hilus behind the seventh rib. Physical examination was not made. There were no symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes.

Recommendation.—Supervision was advised.

MED. II-5.—*Latent Apical Tuberculosis.*—The subject was an American, aged 23. The weight was 100 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was thickening of the apical pleura with salients projecting into the lung at the second interspace and nodules behind the fourth and tenth ribs, and four calcified areas at the hilus. In the left lung, there was a similar pleural thickening. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes with peripheral calcified nodules.

Recommendation.—Supervision was recommended.

MED. II-6.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 24. The weight was 113 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the the right lung, there was a scanty infiltration at the apex in the second interspace. In the left lung, there was a similar infiltration in the second interspace. There were no physical signs or symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was recommended.

MED. II-7.—*Latent Apical Tuberculosis.*—The subject was an American, aged 23. The weight was 81 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a somewhat scanty infiltration at the apex in the second interspace and behind the third rib. In the left lung, there was a similar infiltration at the apex in the second interspace. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was advised.

MED. II-8.—*Latent Apical Tuberculosis.*—The subject was an American, aged 23. The weight was 105 per cent. The tuberculin reaction was + to 1 mg.

Examination.—Roentgenologic examination showed: In the right lung, there were a very small area of scanty infiltration at the apex and a nodule apparently uncalcified in the fifth interspace. In the left lung, there was a moderately dense infiltration at the apex in the second interspace. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis and tuberculous pulmonary nodule was made.

Recommendation.—Semi-annual observation was advised.

MED. II-9.—*Latent Apical Tuberculosis.*—The subject was an American, aged 23. The weight was 94 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a scanty infiltration in the right apex in the second interspace. In the left lung, there was a similar infiltration in the second interspace. The oblique film revealed a calcified area close to the right bronchus. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes.

Recommendation.—Semi-annual observation was recommended.

MED. II-10.—*Latent Apical Tuberculosis.*—The subject was a Polish man, aged 23. The weight was 97 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination revealed a somewhat scanty infiltration at the apex of the right lung in the second and third interspaces. There were no physical signs or symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was advised.

MED. II-11.—*Latent Apical Tuberculosis.*—The subject was an Italian, aged 22. The weight was 95 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed thickening of the apical pleura of the left lung with salients projecting into the lung field in the second interspace and behind the third rib; at the hilus there were three calcified areas with a calcified nodule in the lung at the seventh interspace. There were no physical signs or symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes with a peripheral calcified nodule.

Recommendation.—Supervision was recommended.

MED. II-12.—*Latent Apical Tuberculosis.*—The subject was an American, aged 23. The weight was not recorded. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed a scanty infiltration at the left apex in the second interspace. Physical examination was not done. There were no symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was recommended.

THIRD YEAR

MED. III-1.—*Pulmonary Tuberculosis.*—The subject was an American, aged 24. The weight was 87 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed in the right lung a small area of scanty infiltration at the apex in the second interspace, an area of soft infiltration between the anterior levels of the second and fourth ribs toward the axilla and a calcified nodule at the base. Physical examination revealed limitation of movement at the right base, where the patient had had a dull pain of four days' duration. Three weeks later he became ill with fever and malaise due to pleurisy with effusion on the right side. Contact with tuberculosis was not recorded.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Treatment in a sanatorium was advised.

MED. III-2.—*Pulmonary Tuberculosis.*—The subject was an American, aged 26. The weight was 80 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a scanty infiltration extending as low as the fourth rib. In the left lung, there was a moderately dense infiltration extending as low as the fourth interspace. Physical examination revealed poor but equal expansion on the two sides. Resonance was diminished at both apexes, especially the right. Transmitted voice sounds were increased over the apex of the right lung. On one examination, inconstant râles were heard in this area posteriorly. There were no symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was pulmonary tuberculosis.

Recommendation.—Treatment in a sanatorium was recommended.

MED. III-3.—*Pulmonary Tuberculosis.*—The subject was an American Jew, aged 24. The weight was 89 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a scanty infiltration in the second interspace and a moderately dense infiltration with a small cavity between the fourth and seventh ribs. In the left lung, there was a scanty infiltration in the second interspace and a nodule at the base below the dome of the diaphragm. Physical examination revealed restricted movement and diminished resonance over the infiltrated area on the right. There were no symptoms. This student had had acute osteomyelitis at the age of 4. He had had no known contact with tuberculosis.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Treatment in a sanatorium was advised.

MED. III-4.—*Pulmonary Tuberculosis.*—The subject was an American Jew, aged 22. The weight was 98 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed a moderately dense infiltration at the apex of the left lung, extending as low as the fifth rib. Physical examination revealed diminished resonance over the apex of the left lung, and medium moist râles were heard in a small area in the left interscapular region opposite the scapular spine. The student sometimes had slight expectoration. He had had no known contact with tuberculosis.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Treatment in a sanatorium was recommended.

MED. III-5.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 26. The weight was 106 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed a moderately dense infiltration at the apex of the left lung extending as low as the fifth rib. There were no physical signs. The patient had had influenzal attacks six and four years before this examination, but no other respiratory illness. Contact with tuberculosis was not reported.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was advised.

MED. III-6.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 23. The weight was 94 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed in the right lung a scanty infiltration at the apex in the second interspace and a denser infiltration between the third and fifth ribs; there were three calcified areas at the hilus. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

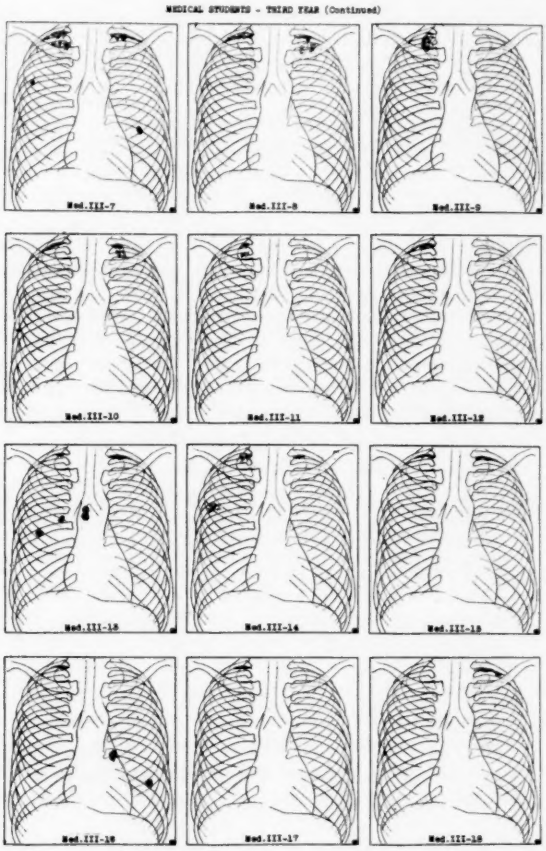


Figure 4.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes.

Recommendation.—Supervision was recommended.

MED. III-7.—*Latent Apical Tuberculosis.*—The subject was an American, aged 26. The weight was 95 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination—Roentgenologic examination revealed: In the right lung, there was a somewhat scanty, soft infiltration at the apex in the second and third

interspaces and a calcified nodule at the sixth rib. In the left lung, there was a thickening of the apical pleura with salients projecting into the lung at the second interspace and behind the third rib. There were no physical signs. The symptoms were not reported. A sister had had pulmonary tuberculosis for sixteen years; her sputum contained tubercle bacilli for two years at the beginning of her illness but had not been known to be positive since.

Diagnosis.—The diagnosis was latent apical tuberculosis and peripheral tuberculous nodules.

Recommendation.—Supervision was recommended.

MED. III-8.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24. The weight was 104 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was an infiltration at the apex in the second interspace. In the left lung, there was an infiltration in the second and third interspaces and behind the third rib. There were no physical signs. The student tired easily. Contact with tuberculosis was not recorded.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was advised.

MED. III-9.—*Latent Apical Tuberculosis.*—The student was an American, aged 23. The weight was 104 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed a moderately dense soft infiltration in the left lung above the clavicle in the second and third interspaces. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was advised.

MED. III-10.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24. The weight was 100 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was thickening of the apical pleura with salients projecting into the lung. In the left lung, there was a scanty infiltration at the apex in the second and third interspaces. There were no physical signs or symptoms. There has been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was recommended.

MED. III-11.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24 years. The weight was 104 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed a scanty infiltration at the apex of the right lung in the second and third interspaces. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was recommended.

MED. III-12.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 96 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed a somewhat scanty infiltration at the apex of the right lung in the second interspace. Physical examination was not made. There were no symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Semi-annual observation was advised.

MED. III-13.—*Latent Apical Tuberculosis.*—The subject was an American, aged 22. The weight was 98 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a small area of infiltration at the apex and a calcified area at the hilus in the sixth interspace with a calcified nodule behind the seventh rib. In the left lung, there was a similar more extensive infiltration in the second interspace; a large calcified area was seen in the oblique film close to the interbronchial angle. There were no physical signs or symptoms. Contact with tuberculosis was not recorded.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes with a peripheral calcified nodule.

Recommendation.—Semi-annual observation was advised.

MED. III-14.—*Latent Apical Tuberculosis.*—The subject was an American, aged 22. The weight was 98 per cent. The tuberculin reaction was + to 1 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a small area of scanty infiltration in the second interspace and a small area of rather scanty infiltration at the level of the sixth rib toward the axilla. In the left lung, there was a small area of scanty infiltration in the second interspace. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was advised.

MED. III-15.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24. The weight was 91 per cent. The tuberculin reaction was + to 1 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was thickening of the apical pleura with salients projecting into the lung in the second interspace. In the left lung, there was a similar pleural thickening with salients. Physical examination was not made. The student complained of constant fatigue. There was no record of contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was recommended.

MED. III-16.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 115 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a very scanty infiltration at the apex in the second interspace. In the left lung, there were a calcified nodule at the base and an area of calcification at the hilus within the shadow of the heart. There were no physical signs or symptoms. This student's father was thought to have pulmonary tuberculosis ten years previously, but tubercle bacilli were not found in his sputum.

Diagnosis.—The diagnosis was latent apical tuberculosis with tuberculosis of the tracheobronchial lymph nodes and a peripheral calcified nodule.

Recommendation.—Semi-annual observation was advised.

MED. III-17.—*Latent Apical Tuberculosis.*—The subject was an American, aged 32. The weight was 94 per cent. The tuberculin reaction was ++ to 0.1 mg.

Examination.—Roentgenologic examination showed thickening of the apical pleura of the right lung with salients projecting into the lung substance in the second interspace. There were no physical signs or symptoms. The student

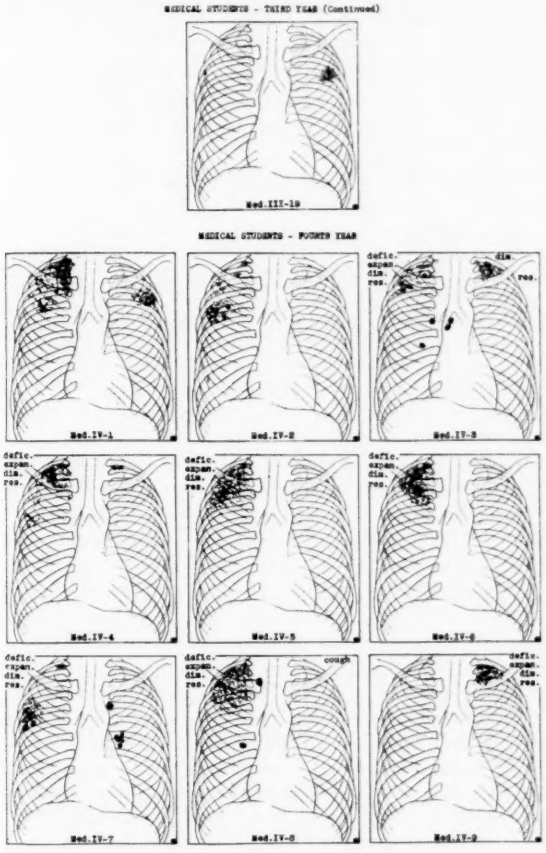


Figure 5.

lived in the same fraternity house as a student with manifest tuberculosis (Med. IV-1).

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Semi-annual observation was recommended.

MED. III-18.—*Latent Apical Tuberculosis.*—This subject was an American, aged 23. The weight was 101 per cent. The tuberculin reaction was + 0.1 mg.

Examination.—Roentgenologic examination revealed thickening of the apical pleura in the left lung with salients projecting into the lung field at the second interspace. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Semi-annual observation was recommended.

Third Year.—MED. III-19.—*Latent Tuberculous Infiltration of the Lung.*—The subject was an American, aged 24. The weight was 101 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed in the left lung an area of somewhat scanty, soft infiltration at the anterior level of the second interspace and the third rib. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent tuberculous infiltration of the lung.

Recommendation.—Supervision was advised.

FOURTH YEAR

MED. IV-1.—*Pulmonary Tuberculosis.*—The subject was a Cuban of Spanish parentage, aged 25. The weight was 116 per cent. A tuberculin test was not made.

Examination.—Roentgenologic examination showed: In the right lung, there was a moderately dense, strandlike infiltration extending from the apex as low as the sixth rib. In the left lung, there was an area of infiltration with a small round shadow suggesting a cavity between the fourth and sixth ribs in the axilla. Physical examination was not performed.

Sputum-positive tuberculosis had developed in this student eighteen months before the examination. He had spent ten months in a sanatorium and had been under medical supervision since discharge. Previous to this illness, he had had no known contact with tuberculosis.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Supervision was advised.

MED. IV-2.—*Pulmonary Tuberculosis.*—The subject was an American, aged 24. The weight was 115 per cent. A tuberculin test was not made.

Examination.—Roentgenologic examination showed on the right side a scanty infiltration as low as the fourth interspace and a moderately dense infiltration between the fifth and seventh ribs toward the axilla. There were no physical signs.

This man had had a hemorrhage nine months before examination, and had spent three months in a sanatorium. He had been under supervision since discharge. He had had no known contact with tuberculosis prior to his illness.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Supervision was advised.

MED. IV-3.—*Pulmonary Tuberculosis.*—The subject was an American, aged 28. The weight was 96 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was an infiltration in the second and third interspaces above the clavicle and in the third and fourth interspaces toward the axilla below the clavicle. There was a calcified nodule behind the fourth rib and another in the eighth interspace with calcified areas at the hilus and at the bifurcation of the trachea. In the left lung, there was an infiltration above the clavicle in the second and third interspaces. Physical examination revealed flattening and restricted movement

at the right apex. There was diminished resonance at both apexes with increased bronchophony on the right. This student had had frequent winter "colds," but had no symptoms when examined. He had had no known contact with tuberculosis.

Diagnosis.—The diagnosis was pulmonary tuberculosis and tuberculosis of the tracheobronchial lymph nodes with peripheral calcified nodules.

Recommendation.—Supervision was advised.

MED. IV-4.—*Pulmonary Tuberculosis.*—The subject was an American, aged 26. The weight was 96 per cent. A tuberculin test was not made.

Examination.—Roentgenologic examination showed: In the right lung, there were moderately dense infiltration above the clavicle and a scanty infiltration below this as low as the seventh rib. In the left lung, there was a small area of infiltration at the apex. Physical examination revealed diminished expansion and resonance over the right apex. Breath sounds were granular with prolonged expiration, and vocal resonance was markedly increased. The student stated that he had had no respiratory infections since an attack of acute bronchitis four years earlier. His temperature, taken afternoon and evening for one week, showed frequent elevations to 99.2 and 99.4 F. For more than two years he had lived in the same fraternity house as the student (Med. IV-1) with manifest tuberculosis, whose case was described.

Diagnosis.—The diagnosis was pulmonary tuberculosis.

Recommendation.—Treatment in a sanatorium was recommended.

MED. IV-5.—*Pulmonary Tuberculosis.*—The subject was an American, aged 28. The weight was 102 per cent. The tuberculin reaction was + 0.01 mg.

Examination.—Roentgenologic examination revealed a moderate dense infiltration at the apex of the right lung extending as low as the sixth rib. Physical examination revealed restricted expansion and diminished resonance at the apex of the right lung with an increased transmission of voice sounds and roughened breath sounds. These were no symptoms, and there had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Supervision was advised.

MED. IV-6.—*Pulmonary Tuberculosis.*—The subject was an American, aged 24 years. The weight was 97 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination revealed a moderately dense, soft infiltration at the apex of the right lung extending as low as the sixth rib. Physical examination revealed slightly diminished expansion and diminished resonance at the apex of that lung. The patient stated that he had not had any severe respiratory infections, but for one week before examination he had had cough with mucopurulent expectoration. This had ceased at the time of examination. His temperature reached 99 F. on several occasions immediately following discovery of the lesion, but remained normal for six weeks afterward. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was pulmonary tuberculosis.

Recommendation.—Treatment in a sanatorium was advised.

MED. IV-7.—*Pulmonary Tuberculosis.*—The subject was an American, aged 26. The weight was 89 per cent. The tuberculin reaction was +++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a moderately dense infiltration in the apex in the second interspace and between the fourth and sixth ribs toward the axilla. In the left lung, there were a nodule and a calcified area at the hilus. Physical examination revealed diminished expansion and diminished resonance over the apex of the right lung

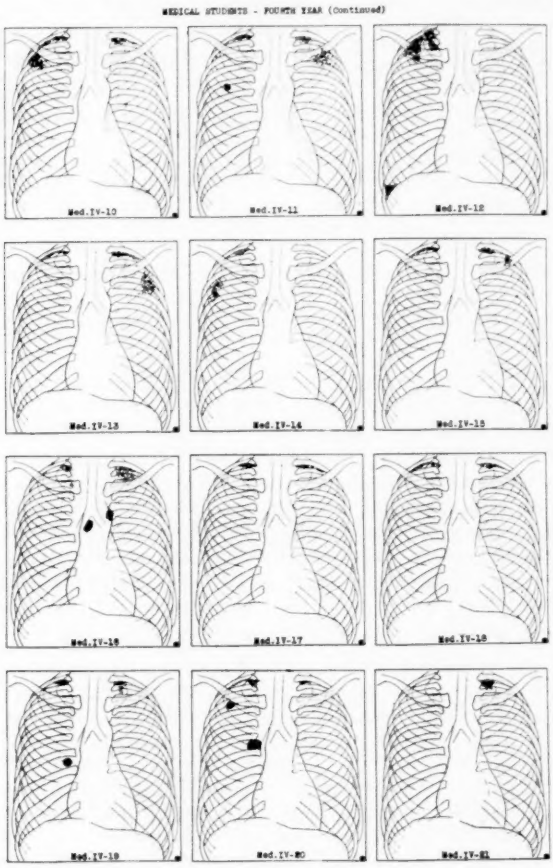


Figure 6.

with increased vocal resonance. There were no râles. The patient stated that he had been troubled by cough in the morning and had occasionally expectorated about one-half drachm (1.9 Gm.) of sputum. He had had no known contact with tuberculosis.

Diagnosis.—A diagnosis of pulmonary tuberculosis and tuberculosis of the tracheobronchial lymph nodes with a peripheral calcified nodule was made.

Recommendation.—Treatment in a sanatorium was recommended.

MED. IV-8.—*Pulmonary Tuberculosis.*—The subject was a Canadian woman, aged 35. The weight was 90 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed a moderately dense infiltration at the apex of the right lung extending as low as the anterior level of the third rib; there were calcified areas at the right hilus and to the right of the trachea. Physicial examination revealed diminished expansion and resonance over the apex of the right lung. The breath sounds were suppressed. There were no râles. The patient stated that for several years she had been troubled by a tickling sensation in the throat resulting in slight cough. She had a slight amount of sputum which she swallowed. Her afternoon temperature reached 99 F. on six occasions during two weeks preceding the onset of menstruation. Her father, who was still alive, had been sent to a western climate thirty years previously for suspected tuberculosis.

Diagnosis.—The diagnosis was pulmonary tuberculosis and tuberculosis of the tracheobronchial lymph nodes.

Recommendation.—Supervision was advised.

MED. IV-9.—*Pulmonary Tuberculosis.*—The subject was an American, aged 27. The weight was 99 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed a moderately dense infiltration at the apex of the left lung in the second and third interspaces above the clavicle. Physical examination revealed diminished movement and loss of resonance at the apex of that lung. There were no symptoms, and there had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of pulmonary tuberculosis was made.

Recommendation.—Supervision was recommended.

MED. IV-10.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 86 per cent. The tuberculin reaction was +++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a moderately dense infiltration at the apex in the second interspace and in the third and fourth interspaces at the axilla. In the left lung, there was a similar infiltration in the second interspace. There were no physical signs. The student had had pneumonia in infancy and frequent "colds" before tonsillectomy one year earlier. His temperature, taken afternoon and evening for one week, did not reach 99 F. He lived in the fraternity house with the student (Med. IV-1) in whom sputum-positive tuberculosis had developed previously.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Treatment in a sanatorium was advised.

MED. IV-11.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24. The weight was 98 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed a rather scanty infiltration at the apex in the second interspace and a nodule in the sixth interspace. In the left lung, there was a scanty infiltration at the apex and between the third and fifth ribs toward the axilla. Physical examination revealed rhonchi in all areas of the chest. This student had had chronic bronchitis with occasional acute attacks for the past four years. His cough was sometimes productive, and he promised to have his sputum examined. He had had no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was advised.

MED. IV-12.—*Latent Apical Tuberculosis.*—The subject was an American, aged 26. The weight was 92 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination revealed a moderately dense infiltration at the apex of the right lung extending as low as the fifth rib; the costodiaphragmatic sulcus was obscured. There were no physical signs or symptoms. Four years before the present examination, this student had had pleurisy with effusion and 1,000 cc. of fluid had been aspirated. He had had no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Treatment in a sanatorium was recommended.

MED. IV-13.—*Latent Apical Tuberculosis.*—The subject was an American, aged 26. The weight was 95 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a shadow of uncertain significance, probably caused by pleural thickening at the apex. In the left lung, there was a scanty infiltration at the apex in the second interspace and behind the third rib, and a more definite infiltration between the third and sixth ribs toward the axilla. There were no physical signs. This student complained of frequent colds with cough and expectoration. There were no symptoms. During four months he was in contact with a brother, who had died of pulmonary tuberculosis about eighteen months before this examination.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was recommended.

MED. IV-14.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24. The weight was 100 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed in the right lung, a scanty infiltration at the apex in the second interspace and a soft ill delimited mottling between the fourth and sixth ribs toward the axilla. There were no physical signs. The student had had frequent coryza and bronchitis up to two years before examination, less frequent since. There were no symptoms. He had had no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was advised.

MED. IV-15.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 84 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a somewhat scanty infiltration at the apex in the second interspace. In the left lung, there was a similar infiltration in the second interspace and at the third rib and interspace toward the lateral wall of the chest. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Supervision was advised.

MED. IV-16.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 76 per cent. The tuberculin reaction was + to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a scanty infiltration at the apex in the second interspace. In the left lung, there was a similar infiltration in the second and third interspaces above the clavicle. There was a calcified area at the left hilus, within the aortic shadow, and a second calcified area was seen in the oblique film situated close to the right bronchus. There were no physical signs or symptoms. The student had been subject to frequent infections of the upper respiratory tract. He had had no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes.

Recommendation.—Supervision was recommended.

MED. IV-17.—*Latent Apical Tuberculosis.*—The subject was an American, aged 24. The weight was 85 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed: In the right lung, there was a scanty infiltration at the apex in the second interspace. In the left lung, there was a similar infiltration in the second interspace. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was recommended.

MED. IV-18.—*Latent Apical Tuberculosis.*—The subject was an American, aged 26. The weight was 92 per cent. The tuberculin reaction was +++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was an infiltration at the apex in the second interspace. In the left lung, there was a similar infiltration in the second interspace. Physical examination was not made. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was advised.

MED. IV-19.—*Latent Apical Tuberculosis.*—The subject was an American, aged 26. The weight was 89 per cent. The tuberculin reaction was +++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a scanty infiltration at the apex in the second interspace and a calcified area in the eighth interspace at the hilus. In the left lung, there was a similar infiltration in the second interspace. Physicial examination was not made. There were no symptoms. Contact with tuberculosis was not reported.

Diagnosis.—A diagnosis of latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes was made.

Recommendation.—Supervision was recommended.

MED. IV-20.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 106 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a scanty infiltration at the apex in the second interspace, a calcified nodule in the fourth interspace and a large calcified mass in the seventh interspace at

the hilus. In the left lung, there was a small area of infiltration in the second interspace. There were no physical signs or symptoms. Contact with tuberculosis was not reported.

Diagnosis.—A diagnosis of latent apical tuberculosis and tuberculosis of the tracheobronchial lymph nodes with a peripheral calcified nodule was made.

Recommendation.—Supervision was advised.

MED. IV-21.—*Latent Apical Tuberculosis.*—The subject was an American Jew, aged 23. The weight was 104 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed a small area of moderately dense infiltration at the apex of the left lung in the second interspace. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

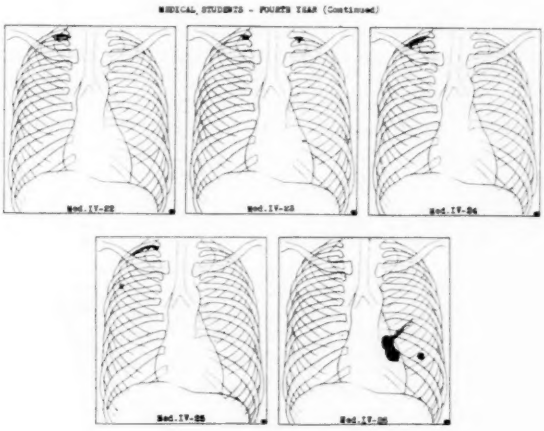


Figure 7.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was advised.

MED. IV-22.—*Latent Apical Tuberculosis.*—The subject was an American, aged 26. The weight was 84 per cent. The tuberculin reaction was + to 0.1 mg.

Examination.—Roentgenologic examination revealed in the right lung a thickening of the apical pleura and an infiltration in the second interspace. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Supervision was recommended.

MED. IV-23.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 79 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed: In the right lung, there was a small area of scanty infiltration at the apex in the second interspace. In the

left lung, there was a similar area of infiltration. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—A diagnosis of latent apical tuberculosis was made.

Recommendation.—Semi-annual observation was advised.

MED. IV-24.—*Latent Apical Tuberculosis.*—The subject, a man, aged 25, was born in Germany of Finnish parents. The weight was 104 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination revealed thickening of the apical pleura in the right lung with infiltration in the second interspace and behind the third rib. There were no definite physical signs and no symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was recommended.

MED. IV-25.—*Latent Apical Tuberculosis.*—The subject was an American, aged 25. The weight was 110 per cent. The tuberculin reaction was ++ to 0.01 mg.

Examination.—Roentgenologic examination showed thickening of the apical pleura in the right lung with sharply defined salients extending into the lung field at the second interspace. Physical examination was not made. There were no symptoms. Contact with tuberculosis was not reported.

Diagnosis.—The diagnosis was latent apical tuberculosis.

Recommendation.—Semi-annual observation was advised.

MED. IV-26.—*Latent Tuberculous Infiltration of the Lung.*—The subject was an American, aged 30. The weight was 117 per cent. The tuberculin reaction was +++ to 0.01 mg.

Examination.—Roentgenologic examination revealed in the left lung a few coarse strands at the anterior level of the third interspace, a nodule at the base and two large faintly calcified areas at the hilus within the shadow of the heart. There were no physical signs or symptoms. There had been no known contact with tuberculosis.

Diagnosis.—The diagnosis was latent tuberculous infiltration of the lung and tuberculosis of the tracheobronchial lymph nodes with a peripheral nodule.

Recommendation.—Supervision was advised.

INFECTIVE NEURONITIS

REPORT OF A CASE WITH AUTOPSY OBSERVATIONS *

HARRY G. JACOBI, M.D.
Associate Attending Physician, Lenox Hill Hospital
NEW YORK

In 1919, Kennedy [1] described four cases which, while presenting all the signs of polyneuritis, showed certain other changes that could not be completely explained on that basis alone. He employed the term infective neuronitis as being more descriptive of the clinical and pathologic picture. A short time previous to Kennedy's paper, Bradford [2] reported a similar group of thirty cases occurring in soldiers. The series included the four cases reported by Kennedy and was described under the heading of infective neuritis. All these cases had a rather acute onset, with fever, headache, sore throat, vomiting and pains in the back and limbs. The headache was usually pronounced and entirely out of proportion to the fever, which subsided after a day or two. A quiescent period of from three days to six weeks then followed, during which the patients were completely free from symptoms. After this quiescent period, all the patients complained of a sudden paralysis involving the lower extremities and confined principally to the large muscles of the proximal segments of the limbs. The suddenness of the paralysis, combined with the absence of neurologic signs of disease, often led at the onset to the diagnosis of malingering. During the course of the illness, the characteristic signs presented by all of the patients were a gradually increasing ascending flaccid paralysis and a facial paralysis, often bilateral and of the infranuclear type. Sensory changes, such as pain, numbness and tingling were noted. At the onset, the reflexes would be intact, but after a period, the knee jerks and abdominal reflexes disappeared. After the initial rise in temperature, the course of the disease was usually afebrile. Tachycardia in varying degree was a rather prominent feature in all the cases. In only four of the cases were tests of the spinal fluid made and found to be negative. A mild leukocytosis was present only at the onset of symptoms. Bradford reported a mortality of 37.5 per cent in his series, one half of these occurring

* Submitted for publication, Feb. 10, 1931.

* From the Medical Service of Dr. A. L. Garbat, Lenox Hill Hospital, N. Y.

1. Kennedy, Foster: Infective Neuronitis, Arch. Neurol. & Psychiat. **11**:621 (Dec.) 1919.

2. Bradford, J. R.: Acute Infective Neuritis, Quart. J. Med. **12**:88, 1918-1919.

within a week from the onset of the palsy. Bashford [3] reported the postmortem observations in seven of the fatal cases. His determinations were similar to ours. Material obtained from two of the fatal cases was used by Wilson [4] for cultural purposes and inoculation into monkeys. At the end of seven days, cultures of this material showed minute semitranslucent colonies on the surface of the agar which grew rapidly after that time and assumed a faint yellow color. By the end of the twelfth to fourteenth day, these colonies had united to form a yellow-brown continuous layer, showing slight elevation on its surface, while the serum agar had become definitely opaque. No strain in subcultures could be carried beyond the fifth generation.

Subdural inoculation into monkeys of the material from the fatal cases gave positive results. Likewise, the transmission of the disease from these monkeys to others was successful in producing both the clinical picture and the pathologic changes observed by Bashford in all the fatal cases. In stained sections, the organism was found to be arranged in pairs or in irregular small groups of from five to eight organisms and, more rarely, in short chains. The organism was not acid-fast and was gram-positive. It was best demonstrated with Löffler's methylene blue (methylthionine chloride, U. S. P.) or polychrome blue after treatment with a mordant, such as tannic or phenol.

REPORT OF A CASE

History.—A white woman, aged 32, who was born in Sweden and had lived in the United States for three and a half years, had been engaged as a masseuse, principally in caring for patients with poliomyelitis. On admission to the hospital, on Feb. 21, 1929, she complained of pain in the muscles of the leg and of inability to move them.

The past and family histories were not of importance. In the past, she occasionally had suffered from headaches and had also been troubled with constipation. She was unmarried, and there was no history of an excessive use of alcohol or tobacco. She was admitted to the hospital with the complaint of weakness of the arms and legs of about two weeks' duration. Her health had been good until the onset of these symptoms, with the exception of an attack of sore throat and fever which she had had about six weeks before. She had recovered from this and had apparently felt well for about four weeks. Then one day, she noticed slight weakness and a tired out feeling in her arms and legs, which became progressively worse. The onset of the symptoms was not sudden, nor was there fever at any time. She was admitted to another hospital, where a complete examination, including a lumbar puncture, was performed, and because of the negative clinical and laboratory observations a diagnosis of hysteria was made.

Examination.—By the time I saw the patient, however (February), considerable change had taken place in her condition. She was unable to move about in bed or sit up. There was some rigidity of the neck. Speech, smell, taste and

3. Bashford, E. F.: Quart. J. Med. **12**:104, 1918-1919.
4. Wilson, J. A.: Quart. J. Med. **12**:119, 1918-1919.

hearing were unaffected. The rate of respiration was 22; the pulse was 84, and the temperature, 98.4 F. The pupils were normal and reacted to light and in accommodation. There was a distinct lateral nystagmus but no strabismus. A tremor of the tongue was present. The tonsils were large and very cryptic. Heart action was normal, with an occasional extrasystole. There were no murmurs. The lungs were normal. The abdomen was soft, and no masses or areas of tenderness were present. The liver and the spleen were not felt. There was a loss of muscular power of both the upper and lower extremities. The muscles were painful, and there was a complete absence of all the tendon reflexes. The ankle jerk and plantar reflexes were absent. The abdominal reflexes were present, but easily exhaustible. The sense of touch, pain, heat and cold were preserved, the deep muscle and joint sense were absent. Examination of the eyegrounds gave negative results.

Several examinations were made of the spinal fluid. On February 21, lumbar puncture showed the pressure to be slightly increased, the fluid was clear and 12 cc. was removed for examination. This showed no increase in cells, no globulin, a negative Wassermann reaction and colloidal gold curve and no growth from culture. Reducing substances were absent. On February 28 and March 5, examinations of the spinal fluid were repeated with identical results. Roentgen examination showed the right ethmoid cells to be cloudy as compared to those on the left. The right antrum also showed some haziness. Roentgenograms of the teeth showed apical rarefaction of the lower central and of the upper lateral incisors. The Wassermann reaction of the blood was negative. The blood count on February 22 showed: red blood cells, 4,800,000, and hemoglobin, 70 per cent (Sahli); white blood cells, 8,200; polymorphonuclears, 74 per cent, and lymphocytes, 26 per cent. Examinations were repeated about every four days without any change being noted. Chemical analysis of the blood performed on April 17 showed urea nitrogen, 10.3 mg.; creatinine, 0.5 mg.; uric acid, 1.6 mg., and sugar, 100 mg.; the carbon dioxide-combining power of the blood plasma was 59.5 per cent by volume. On May 11, another chemical analysis of the blood was performed with practically the same results. Urinalysis and cultures from the urine gave negative results.

Course.—On February 26, an attempt was made to determine the electrical response of the muscles of the extremities in order to determine the reaction of degeneration. This was not satisfactory because of the hyperesthesia of all the muscles of the extremities. On February 29, the patient still complained of pain in the muscles. The grasp of the hand and active motions of the arm were not as vigorous as they had been during the last few days. The sternocleidomastoid muscle appeared to be weak. On March 4, the upper left eyelid was noted to lag behind its fellow, and the left brow appeared somewhat higher than the right. There was a slight weakness of the internal rectus muscle of the left eye. There was also a flattening of the left side of the face. On March 6, the patient complained that for the past two or three days she had at times experienced difficulty in breathing and a sensation of obstruction in the throat. On March 11, stimulation of the muscles yielded a brisk response to the faradic current. On March 27, Horner's syndrome could be detected on the right side. There was evidence of general peripheral neuritis and also of involvement of the anterior roots of the cord in addition to involvement of the anterior cells. No abdominal reflexes were present. There was a loss of vibratory sense in the legs, arms and hands. The sense of position in both feet and in the right hand was absent. On April 2, a loss of the pharyngeal reflex was also noted. The pulse had become much more rapid and ranged between 110 and 150, while the temperature and respirations

remained normal. The patient now complained of diplopia and difficulty in swallowing. There was some loss in the rectal and bladder control.

The patient's condition became steadily worse. The temperature soon showed a steady rise, which was accounted for by the presence of signs of a diffuse, terminal bronchopneumonia.

Necropsy Findings.—The diagnosis was: bilateral bronchopneumonia and atelectasis; brown atrophy of the heart and liver; cholelithiasis and chronic cholecystitis; acute splenic tumor, and cloudy swelling of the kidneys.

The dura and pia mater showed no changes. The cerebral cortex showed marked congestion and a slight diffuse infiltration of small round cells. This infiltration was also present in the pons and subthalamic regions. The cerebrum showed a reduction in the Purkinje cells and marked degenerative changes in those present. A marked reduction in the cerebellar cells was also noted.

The entire spinal cord showed degenerative changes in the anterior horn cells, the nerve fibers, the spinal ganglion cells and the sensory neurons of the tracts of Goll and Burdach. A slight, diffuse, small round cell infiltration was present. No perivascular collars were noted. The lesion was that of a diffuse degeneration of neurons, accompanied by a low grade chronic inflammation.

COMMENT

Clinically, these cases of infective neuronitis are characterized by a gradually increasing paralysis, insidious in onset and suggesting an infectious process as the causative factor. At varying intervals after an indefinite, acute, febrile reaction, muscular paralyses are noted, beginning usually with those of the lower extremities, unaccompanied by any temperature reaction, and involving the proximal rather than the distal groups of muscles. At some period during the course of the disease, there occur a facial paralysis and a constant sensation of obstruction in the throat. The latter manifestation is regarded by Kennedy as due to a specific action of the infecting agent, analogous to the occurrence of trismus in tetanus and oculomotor palsy in diphtheria. Usually, there are signs of involvement of the spinal roots as evidenced by diminished sphincter control and loss of sensation in the areas of distribution of the lower sacral segments. Changes in the posterior tracts also occur, which may account for the extreme pain on pressure which these patients complain of, especially during the early part of the disease; these changes subsequently result in the loss of vibratory sensibility and that in the deep muscles and joints. In addition, the usual signs and changes noted in peripheral neuritis are also present. Thus, it will be noted that cases of infective neuronitis have many of the easily recognizable symptoms of acute polyneuritis as well as unmistakable evidence of involvement of the spinal roots and of the central nervous system. One should therefore be sufficiently familiar with their identity to differentiate them properly from the various conditions with which they are apt to be confused, namely, polyneuritis, poliomyelitis, polio-encephalitis and Landry's paralysis.

Pathologically, the disease is characterized by the presence of widespread changes in the posterior ganglions, spinal roots, ventral cornual cells and Betz cells of the cortex, and is thus separated from the neuritides proper. Studies of the pathologic material in the case reported here gave results similar to those obtained by Bashford. These studies showed a patchy neuritis in the peripheral nerves and a degeneration of the cells in the ventral and dorsal cornua, and especially in the cells of the posterior ganglions. Similar, but more benign, changes are found in the deeper layers of the cerebral cortex and in the cells of the pontile nuclei. A small round cell infiltration was found around the ganglion and cornual cells, but not around the meningeal vessels and capillaries, as is usual in poliomyelitis. The ependyma of the spinal central canal showed constant extensive proliferation. The meninges were normal. Thus far, the various laboratory tests of the blood and spinal fluid in such cases have failed to reveal anything that could be described as characteristic of this disease. The isolation, however, of the infecting organism and its successful transmission to animals, as demonstrated by Wilson,[4] establishes infective neuronitis as a clinical entity and warrants further studies.

119 East Eighty-Fourth Street.

THE CUTANEOUS HISTAMINE REACTION AS A TEST FOR COLLATERAL CIRCULATION IN THE EXTREMITIES *

G. DE TAKÁTS, M.D.
CHICAGO

PREVIOUS LITERATURE

When histamine is brought in contact with the minute vessels of the skin, a marked vasodilatation occurs in the normal individual. This reaction has been described by Eppinger [1] and by Sollmann and Pilcher [2] in man. The voluminous literature on the action of histamine on vessels was critically reviewed by Hess. While the minute vessels, capillaries, smallest arterioles and venules dilate under the action of histamine, there is a vasoconstrictor action on the larger arteries and veins.[3] The response of the vessels of the skin to histamine has been extensively studied by Sir Thomas Lewis,[4] who described a triple response to histamine. When a solution of histamine acid phosphate in a concentration of 1:1,000 was placed on the skin and punctured into the epidermis with a fine hypodermic needle, the following reactions resulted: (1) a purplish spot around the puncture, (2) a wheal that usually covered the purplish spot and (3) a red arterial flare around the wheal.

In studying the nature of these phenomena, Lewis concluded that a primary dilatation of the minute vessels accounts for the purplish spot, that a locally increased permeability of the walls of the vessels results in the wheal, and that the flare is brought about by a widespread dilatation of the contiguous strong arterioles due to a local nervous reflex. As in my clinical work I was primarily interested in the flare, it may not be amiss to cite some of Lewis' experiments relating to the flare. A flare may occur after various cutaneous stimuli, such as a pin prick, a scratch, freezing, burning and the histamine puncture; however, none of these agents produces the flare in skin the nerves of which

* Submitted for publication, Feb. 20, 1931.

* From the Peripheral Circulatory Clinic, Department of Surgery, Northwestern University Medical School.

1. Eppinger, Hans: Ueber eine eigentümliche Hautreaktion, hervorgerufen durch Ergamin, Wien. med. Wchnschr. **63**:1413, 1913.

2. Sollmann, T., and Pilcher, J. D.: Endermic Reactions, J. Pharmacol. & Exper. Therap. **9**:309, 1917.

3. Hess, R. W.: Die Regulierung des Blutkreislaufes, Leipzig, Georg Thieme, 1930.

4. Lewis, Thomas: The Blood-Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

have been cut or after enough time has elapsed for degeneration of the nerve to take place. A freshly cut nerve did not prevent the development of a flare. Thus Lewis assumed a local "axon reflex" with an afferent pathway, which is probably sensory, and an efferent vasomotor path. Following cervical sympathectomy, even when enough time had elapsed for degeneration, the reaction was still present.[5] Ebbecke[6] found, however, that this sensory axon reflex, which may be a defense mechanism for the skin and the conjunctiva, is not elicited on the surface of the abdominal viscera.

A clinical application of the histamine response was suggested by Starr.[7] He later reported a study of the histamine reaction in 100 diabetic patients; he found that "the reaction of the skin to histamine, together with the physical findings permitted the demonstration of the presence or absence of adaptations to compensate for sclerotic narrowing of the large arteries and allowed the clinical detection of pathologic change in the minute vessels, when the larger arteries are not notably involved."[8]

Following the stimulating publications of Lewis, independently from Starr, my associates and I showed in previous papers[9] that the histamine reaction offers a rapid clinical test for determining the adequate inflow of arterial blood in patients afflicted with varicose veins, arteriosclerotic and diabetic gangrene or Buerger's disease. It was also suggested that the test might help to determine the height of amputation, by indicating the lowest possible level of adequate cutaneous circulation.

In this paper I wish to report a summary of three years' experience with this test, which was used as a routine measure in the clinic in all suspected and frank cases of peripheral circulatory disturbance.

TECHNIC

The area of skin to be tested was gently swabbed with alcohol, all rubbing being avoided, as it might produce hyperemia. The histamine, preferably put up

5. Kohler, R., and Weth, G.: Die Wirkung der cervicalen Sympathektomie auf die Angina pectoris und die Ausfallserscheinungen nach diesem operativen Eingriff, Ztschr. f. klin. Med. **99**:205, 1924.

6. Ebbecke, U.: Die lokale Gefässreaktion der Haut und der inneren Organe, Arch. f. d. ges. Physiol. **169**:1, 1917.

7. Starr, Isaac, Jr.: Change in the Reaction of the Skin to Histamine, J. A. M. A. **90**:2092 (June 30) 1928.

8. Starr, Isaac, Jr.: Studies on the Circulation of the Feet in Diabetes Mellitus, with and without Gangrene, Am. J. M. Sc. **180**:149, 1930.

9. de Takats, G.; Quint, H.; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**:671 (Feb.) 1929. de Takats, G., and Quint, H.: The Injection Treatment of Varicose Veins, Surg., Gynec. & Obst. **50**:545, 1930.

in 1 cc. ampules in a dilution of 1:1,000,[10] was drawn into a hypodermic syringe through a hypodermic needle. The original technic of Lewis, also used by Starr, of dropping the solution on the skin and puncturing the skin through the solution, was abandoned in favor of intradermal injections, except in special instances in which the study of the wheal was important. So long as I was interested only in the flare, 0.1 cc. of the solution was injected intradermally. The extremity to be tested must be in the horizontal position and the areas of skin under tension above; bony prominences are avoided, as they naturally may give a poor response. On the lower extremity, which was most frequently tested, the injections of histamine were made into the dorsum of the foot, just above the inner side of the ankle, at the middle of the calf, below and above the knee and, if necessary, at the upper third of the thigh. Originally three readings were made at five, ten and fifteen minutes, but it was found sufficient to make one reading at the end of ten minutes. The findings were then tabulated, as shown in previous communications (fig. 1). In the newer charts, I have tabulated these reactions on the basis of 0 to 3, indicating no, faint, fair and marked reaction.

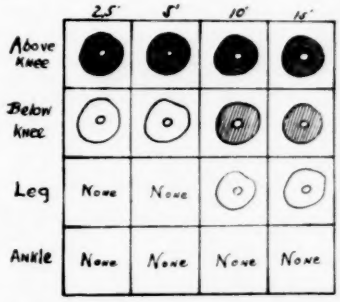


Fig. 1.—Results of histamine test in a diabetic patient with many varicosities of the right leg. A fair pulse was present in the dorsalis pedis and the posterior tibial arteries.

EVALUATION OF METHOD

In order to estimate the value of this method, I tested four groups of subjects, comparing the histamine reaction with other recognized methods of circulation. The groups were as follows:

Group 1: Normal young persons, or patients in whom no disturbance of arterial circulation was suspected. This group served as a control and to show the limits of individual variations.

Group 2: Patients with manifest, fully developed arterial occlusion.

Group 3: Patients with early, clinically hardly recognizable impairment of the arterial circulation. This group was used to demonstrate the comparative value of the test for early recognition.

Group 4: Patients with local or generalized spasticity of the cutaneous vessels. Such patients might show absent or delayed reactions in spite of an adequate arterial inflow.

10. The Eli Lilly Company supplied such ampules for clinical trial.

Group 1.—In this group, 50 subjects, either healthy medical students or young patients afflicted with varicose veins or thrombophlebitis, were studied. A typical record is shown in figure 2. In each instance a positive reaction to histamine was obtained. There was considerable individual variation as to the grade of reaction. Fair haired persons

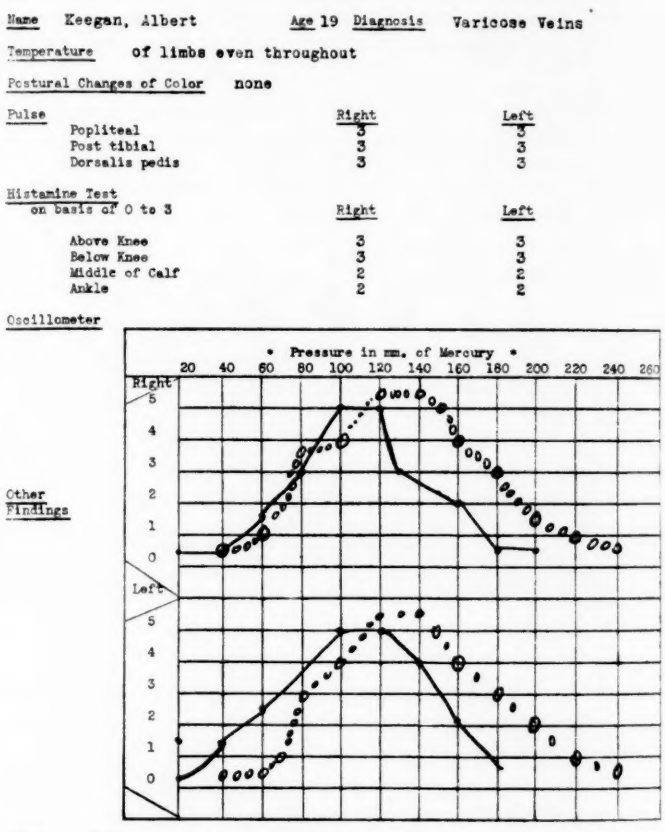


Fig. 2.—Peripheral circulation record. The continuous line indicates the oscillations below the knee; the circle line, those above the knee.

with white, transparent skin gave a stronger response than the darker, more pigmented patients. The flare was invisible on the dark-colored patients. A delay in the appearance of the arterial flare was frequently observed around the ankles. It seemed to indicate that even under physiologic conditions the skin around the malleoli had a poorer circu-

lation than areas higher up on the calf or on the dorsum of the foot. Again, the toes often showed a delayed response. Such a delay was interpreted to be due to a vasoconstriction and may be relieved by warming the foot in blankets, or, as Ipsen has shown with temperature readings, under general anesthesia.[11] The delay of the histamine flare at the periphery of the extremity seems physiologic. It was observable in 35 of the 50 cases. Nevertheless, a definite flare was present in the entire group at the end of ten minutes.

Compared with other methods of circulatory efficiency, the temperature of the skin showed a gradual fall toward the periphery. So long as the fall is gradual, it has no pathologic significance. Benedict and his co-workers[12] showed a decreasing temperature gradient from the trunk to the distal areas of the hands and feet. Subjects with "cold feet" have a poor vasomotor control of the acral regions.[13] A temperature of 25 C. (77 F.) for the first toe may be obtained in normal subjects. The older the patient, the more significant is a sudden fall in temperature, particularly when it occurs above the ankle.

In examining these 50 cases for changes in color during dependent and elevated positions, no case of dependent rubor or of pallor on elevation was found.

The peripheral pulses were not palpable in 3 cases. One patient had a marked phlebitic induration around the inner part of the ankle, which interfered with palpation. One woman had a great deal of fat, as well as bursae, around the ankle. A third patient was edematous. All 3 had normal pulsation in the dorsalis pedis artery.

The oscillometric reading in this normal group showed that no value can be placed on the size of oscillations alone, as this will vary with the cardiac impulse, the tonus of the vessels, the size of the limb and the condition of the soft parts (soft or hard edema). That a maximal oscillation below 2 did not occur in any of these cases is probably of significance.

The normal group also afforded an opportunity to study factors affecting the histamine response. Immersion in hot water accentuates, and in cold water diminishes, the reaction. Elevation of the limb diminishes, and the dependent position increases, the flare. Constriction of the limb above systolic blood pressure prevents the appearance of the flare, which, however, appears as soon as the cuff pressure is lowered

11. Ipsen, Johs: Des methodes qui permettent d'étudier les fonctions des artères peripheriques, Acta chir. Scandinav. **65**:226, 1930.

12. Benedict, F. G.; Miles, W. R., and Johnson, Alice: The Temperature of the Human Skin, Proc. Nat. Acad. Sc. **5**:218, 1919.

13. Brown, G. E.; Allen, E. W., and Mahorner, H. R.: Thrombo-Angiitis Obliterans, Philadelphia, W. B. Saunders Company, 1928.

below systolic pressure. Passive hyperemia, with from 40 to 60 mm. of mercury in the cuff, does not interfere with the histamine reaction.

All these observations were previously described by Lewis.[4] Of great interest to me were my observations made during a chill caused by foreign protein, which showed an absence of the histamine flare,

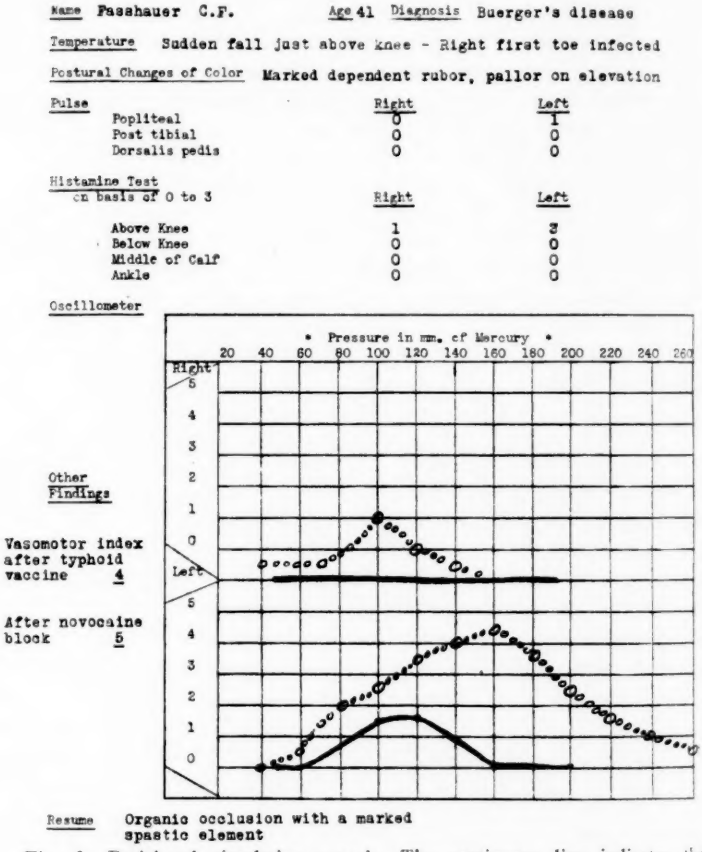

Name Fasshauer C.F. Age 41 Diagnosis Buerger's disease
Temperature Sudden fall just above knee - Right first toe infected
Postural Changes of Color Marked dependent rubor, pallor on elevation
Pulse
Right
Left
Popliteal 0 1
Post tibial 0 0
Dorsalis pedis 0 0
Histamine Test on basis of 0 to 3
Right
Left
Above Knee 1 3
Below Knee 0 0
Middle of Calf 0 0
Ankle 0 0
Oscillometer
Pressure in mm. of Mercury
20 40 60 80 100 120 140 160 180 200 220 240 260
Right
Left
Other Findings
Vasomotor index after typhoid vaccine 4
After novocaine block 5
Resume Organic occlusion with a marked spastic element

Fig. 3.—Peripheral circulation record. The continuous line indicates the oscillations below the knee; the circle line, those above the knee.

and under spinal anesthesia, an exaggeration of the response was elicited. Both observations indicated a modification of the histamine reaction by spasm of the minute vessels.

Group 2.—In this group, 25 patients with manifest, fully developed arterial occlusion were studied. There were 15 patients with arterio-

sclerotic and 5 with diabetic gangrene, and 5 had Buerger's disease. A typical record of this group is shown in figure 3.

The histamine reaction was negative below a certain level in every instance. The temperature of the skin showed a sudden fall, which was well demonstrable on the palm of the hand. On elevation, dependent rubor and pallor were observed, although not consistently of equal degree. The peripheral pulse was absent in all but 1 case of Buerger's disease, in which an excellent collateral circulation had permitted a palpable pulse of the dorsalis pedis. The oscillometer did not show oscillations at certain levels, but sometimes increased oscillations above the arterial occlusion. This increased oscillation was interpreted as an attempt to produce adequate collateral circulation and has great theoretical significance.

The histamine reaction in this group was found valuable in demonstrating improvement under treatment. Thus, in F. J., aged 31, who was affected with Buerger's disease, the histamine flare was absent below the knee and + 3 above the knee. Following a course of treatment with typhoid vaccine, which resulted in marked clinical improvement, the histamine flare became visible as far as the middle third of the lower part of the leg. In every case of Buerger's disease, in which superimposed spasm occurred, the histamine reactions improved with treatment.

The most important function of the histamine test in this group was to determine the level of amputation in cases in which it was indicated. While a positive flare may not ensure one of enough circulation to take care of the healing of the stump,[8] a negative flare certainly warns one against amputating too low. Other tests of circulatory sufficiency have to be used to outline a definite height of amputation. The sudden fall in temperature coincides remarkably with the negative histamine flares. The oscillometer, on the other hand, informs one of the amplitude of the peripheral pulse at a given level and is more helpful in determining the site of obstruction in the artery than in measuring the adequacy of collateral circulation. The oscillometer of Pachon gives a numerical expression of the peripheral pulse wave transmitted to a sensitive aneroid barometer.[14] Obviously, the oscillometer and the histamine reaction measure different phases of the inflow of blood. The oscillometer registers the expansion of the wall of the large vessel and the transmitted wave to the soft parts of the limb. When the wall of the vessel is quite rigid or the soft parts are indurated as a consequence of an old phlebitis, the oscillations may be diminished, and yet the histamine response is normal, as enough blood

14. Samuels, S. S.: The Value of Oscillometry in the Study of the Circulatory Disturbances of the Extremities, J. A. M. A. **88**:1780 (June 4) 1927.

reaches the cutaneous vessels. A case in point was that of Andrew McC., aged 31, in whom thrombophlebitis of the left leg developed following influenza. The largest oscillations below the knee did not exceed 2½ points, whereas in the right leg they exceeded 5 points. Pulsations and the histamine reaction were normal. The diminution of oscillations was interpreted to be due to a lack of expansion in the soft parts. A well palpable, indurative edema of the lower part of the left leg was present.

On the other hand, patients with thrombophlebitis may show signs of diminished inflow with both the oscillometer and the histamine reaction. One such patient was mentioned in a previous communication.[15] Since then, another patient presented herself with typical deep venous thrombosis, cold pulseless feet, markedly diminished oscillations and a negative histamine reaction. It is fair to assume that massive venous thrombosis may give rise to a spastic or even an organic occlusion of the adjacent artery. Histologic evidence in such a case was reported by French observers.[16]

In a case of Buerger's disease, that of A. Sz., aged 48, on whom amputation had been previously performed at the upper third of the lower part of the left leg, there were no oscillations below the knee and none at the middle of the thigh. The histamine reaction was absent below the knee and present after fifteen minutes on the thigh. The femoral artery was palpable below Poupart's ligament. The middle portion of the thigh probably represented the point of occlusion, and hence there were no transmitted pulsations, but the skin reaction was positive, as a collateral blood supply was obtained from a higher level (fig. 4).

In another case of Buerger's disease, that of James M., aged 36, a complete agreement was found between the reaction to histamine and the oscillometric readings, except that the latter gave a more exact degree of circulatory impairment. In spite of the marked pathologic changes on the left side, it was interesting to note the effort to throw blood into the diseased extremity by demonstrating a pulse wave at 260 mm. of mercury. Even as high as at 300 mm. of mercury, oscillations amounting to 1½ were present (fig. 5).

In a case of thrombosis of the right femoral artery following influenza (that of Walter Shr., aged 48), the oscillometer gave a completely negative result from the middle of the thigh down. The histamine reaction became negative at a slightly lower level. Above the obstruction, both the oscillometer and the histamine gave unusually strong

15. de Takats, Quint, Tillotson and Crittenden (footnote 9, first reference).

16. Labbé, M.; Heitz, J., and Dreyfus, Gilbert: Des oblitérations artérielles à point de départ veineux, Presse méd. **38**:217 (Feb. 12) 1930.

reactions. This phenomenon is frequently observed above the level of occlusion and corresponds to an increased pulsation of the artery above the obstruction. In a case cited by Ipsen,[11] that of a woman, aged 75, with arteriosclerotic occlusion, there was no oscillation below the knee and maximal oscillations of 5 above the knee. Five months after

Name Andrew Sz. Age 48 Diagnosis Buerger's disease

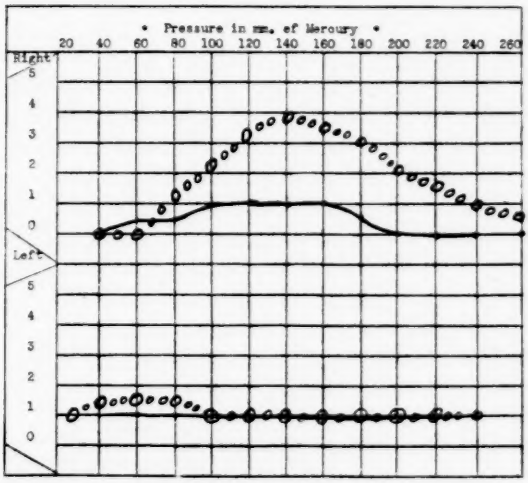
Temperature Sudden fall at midthigh, left, lower leg on right

Postural Changes of Color Left leg amputated - Right, slight rubor

Pulse	Right	Left	
Popliteal	1	0	Femoral present
Post tibial	0	-	
Dorsalis pedis	0	-	

Histamine Test on basis of 0 to 3	Right	Left
Above Knee	3	1
Below Knee	1	-
Middle of Calf	1	-
Ankle	2	-

Oscillometer



Other Findings

Resume Right: Diminution of circulation below knee
Left: Negative oscillations both below and above knee. Histamine and skin temperature indicate adequate collateral circulation above mid thigh

Fig. 4.—Peripheral circulation record. The solid line indicates the oscillations below the knee; the circle line, those above the knee.

amputation, in the presence of a firmly healed femoral stump, the oscillations did not exceed one-half point. The increase of pressure above the obstruction has become unnecessary.

The reactions to the histamine test may not follow closely the changes in the oscillometric readings, as is shown by the following

case. F. J., aged 32, had Buerger's disease, with a typical intermittent claudication, dependent rubor and pallor on elevation. There was a small ulcer at the right big toe. Below the right knee there were no oscillations, and the histamine reaction was positive only above the knee. Following intensive treatment with heat, alternate baths, diathermy

Name James M. Age 36 Diagnosis Buerger's disease

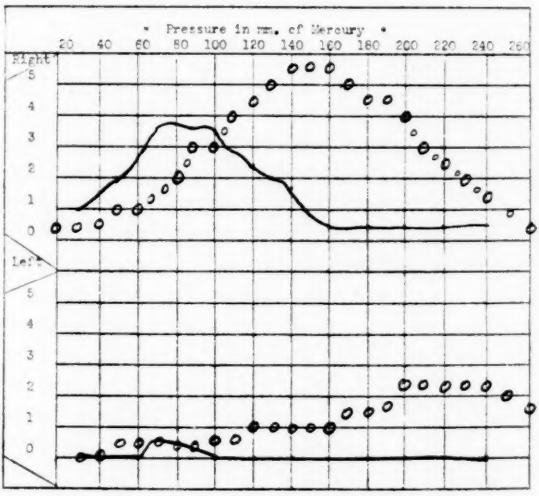
Temperature Right: sudden fall above ankle. Left: just above knee

Postural Changes of Color Typical dependent rubor on left

Pulse	Right	Left
Popliteal	3	0
Post tibial	0	0
Dorsalis pedis	0	0

Histamine Test on basis of 0 to 3	Right	Left
Above Knee	3	3
Below Knee	2	0
Middle of Calf	2	0
Ankle	1	0

Oscillometer



Other Findings

Resume Right: Normal circulatory conditions above ankle
Left: Circulation below knee very poor - effort of compensation above knee

Fig. 5.—Peripheral circulation record. The solid line indicates the oscillations below the knee; the circle line, those above the knee.

and typhoid vaccine, the subjective symptoms were greatly alleviated. The small ulcer healed. The histamine reaction became positive at the middle of the lower part of the leg. The oscillometric readings, however, did not change; the main vessels remained occluded (fig. 6).

Normal reactions may be found at a lower level than the oscillations would indicate, as the blood supply of the skin always extends beyond the level of occlusion in the main vessel. There may also be a normal histamine reaction when the pulsations do not swing the aneroid of the oscillometer, because the soft tissues are rigid, because the wall of

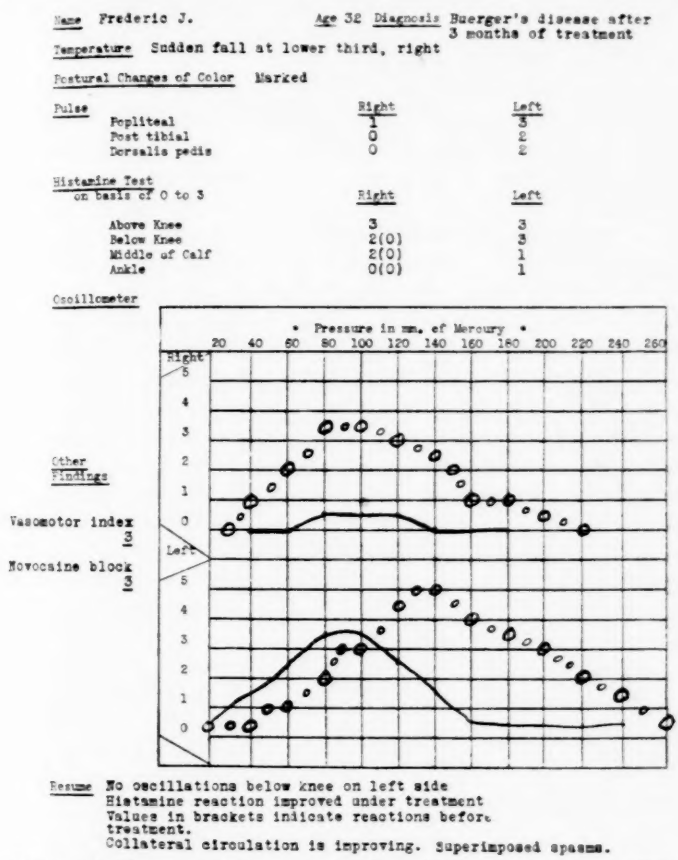

Name Frederic J. Age 32 Diagnosis Buerger's disease after 3 months of treatment
Temperature Sudden fall at lower third, right
Postural Changes of Color Marked
Pulse
Right
Left
Popliteal 1 3
Post tibial 0 2
Dorsalis pedis 0 2
Histamine Test on basis of 0 to 3
Right
Left
Above Knee 3 3
Below Knee 2(0) 3
Middle of Calf 2(0) 1
Ankle 0(0) 1
Oscillometer
Pressure in mm. of Mercury
20 40 60 80 100 120 140 160 180 200 220 240 260
Right
Left
Other Findings
Vasomotor index 3
Novocaine block 3
Resume No oscillations below knee on left side
Histamine reaction improved under treatment
Values in brackets indicate reactions before treatment.
Collateral circulation is improving. Superimposed spasms.

Fig. 6.—Peripheral circulation record. The solid line indicates the oscillations below the knee; the circle line, those above the knee.

the vessel has lost its elasticity or because the occlusion has been well compensated by collateral circulation. One can only emphasize and confirm the opinion of McKittrick and Pratt,[17] that changes in tem-

17. McKittrick, L. S., and Pratt, T. C.: The Operative Treatment of Lesions of the Lower Extremities in Diabetes Mellitus, Arch. Surg. **21**:555 (Oct.) 1930.

perature, elicited with the back or with the palm of the hand, are of importance in estimating collateral circulation. The changes in the temperature of the skin and the histamine flares show almost completely identical levels. Thus in the case of Mrs. A. P., aged 73, who had arteriosclerotic gangrene of the left big toe, there was a sudden fall in temperature at the upper third of the thigh, an unusually high level. The histamine reaction at this point became negative. There was no femoral pulse, and no oscillations on the thigh.

In this group of patients with fully developed arterial occlusion, the question of amputation frequently arose. It seemed important to examine whether the histamine reaction was of any service in the indications for amputation and for the level of amputation. The histamine reaction should not be used alone to determine this point. It is still true that clinical observations, such as the pulse, color and temperature of the leg, are most important in making a decision. However, it gives one a feeling of assurance to have the histamine reaction and the oscillometer back up one's not always infallible clinical observations.

Group 3.—This group consisted of patients with early, clinically hardly recognizable impairment of the arterial circulation. There were 20 patients in this series, although the number could be multiplied indefinitely by the inclusion of older patients seen in the clinic for patients with varicose veins. All diabetic patients with peripheral arteriosclerosis are in danger of circulatory disturbances, and the same is true of the purely arteriosclerotic group. While only 163, or 4.08 per cent, of the 4,066 diabetic patients admitted to the New England Deaconess Hospital required operation for gangrene or infection of the lower extremities,[18] only one third of Starr's unselected 100 diabetic patients had a normal circulation in their feet.[8] A systematic examination of older patients with arteriosclerosis revealed a frequent impairment of circulation, particularly when signs of cardiac weakness, such as a fall in blood pressure, appeared. An examination of the peripheral circulation in diabetic and arteriosclerotic patients who do not have frank symptoms has considerable value. It is in this stage that conservative measures may save the limb.

The histamine reaction in this group was either absent or greatly delayed at the foot and the ankle. As seen in the second group, the fall in the temperature of the skin ran closely parallel with the changes in the response to histamine. Postural color changes were not observed or were very slight; they were certainly not marked enough to be of any assistance. The peripheral pulse was palpable in 15 of 20 patients; however, the absence of pulse, as previously pointed out, does

18. McKittrick, L. S., and Root, H. W.: Diabetic Surgery, Philadelphia, Lea & Febiger, 1928.

not mean that an adequate collateral circulation could not have developed. The oscillometric readings were variable, but the oscillations were generally diminished. So much depends on the amount of vasoconstriction that a simple oscillometric reading did not determine the actual amount of organic obstruction in this group. This factor of vascular spasm will be discussed later.

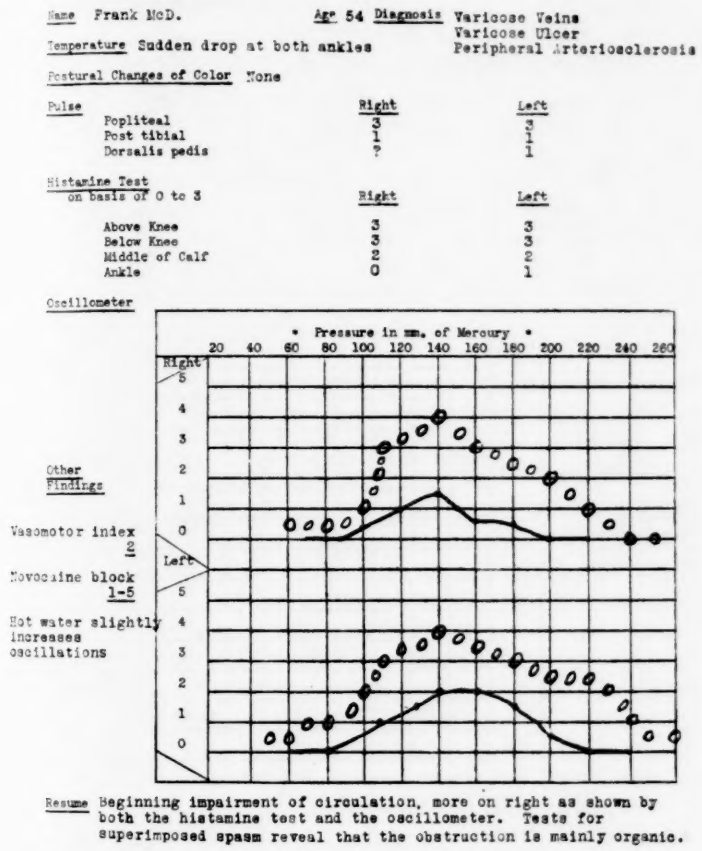

Name Frank McD.
Age 54 Diagnosis Varicose Veins
Varicose Ulcer
Peripheral Arteriosclerosis
Temperature Sudden drop at both ankles
Postural Changes of Color None
Pulse
Right
Left
Popliteal 3 3
Post tibial 1 1
Dorsalis pedis ? 1
Histamine Test on basis of 0 to 3
Right
Left
Above Knee 3 3
Below Knee 3 3
Middle of Calf 2 2
Ankle 0 1
Oscillometer
Pressure in mm. of Mercury
20 40 60 80 100 120 140 160 180 200 220 240 260
Right
Left
Other Findings
Vasomotor index 2
Novocaine block 1-5
Hot water slightly increases oscillations
Resume Beginning impairment of circulation, more on right as shown by both the histamine test and the oscillometer. Tests for superimposed spasm reveal that the obstruction is mainly organic.

Fig. 7.—Peripheral circulation record. The solid line indicates the oscillations below the knee; the circle line, those above the knee.

The histamine response in this group quickly showed the clinician that the peripheral circulation was impaired. Whether or not there is a superimposed vascular spasm must be determined by measures to be described.

A typical chart of this group is presented in figure 7.

Group 4.—It is well known that vascular spasms may give rise to serious circulatory disturbances. Some of the spasms occur in anatomically intact vessels, whereas they also may be superimposed on organic arterial obstructions, particularly in the early stages of Buerger's disease. It seemed important to determine the behavior of the histamine

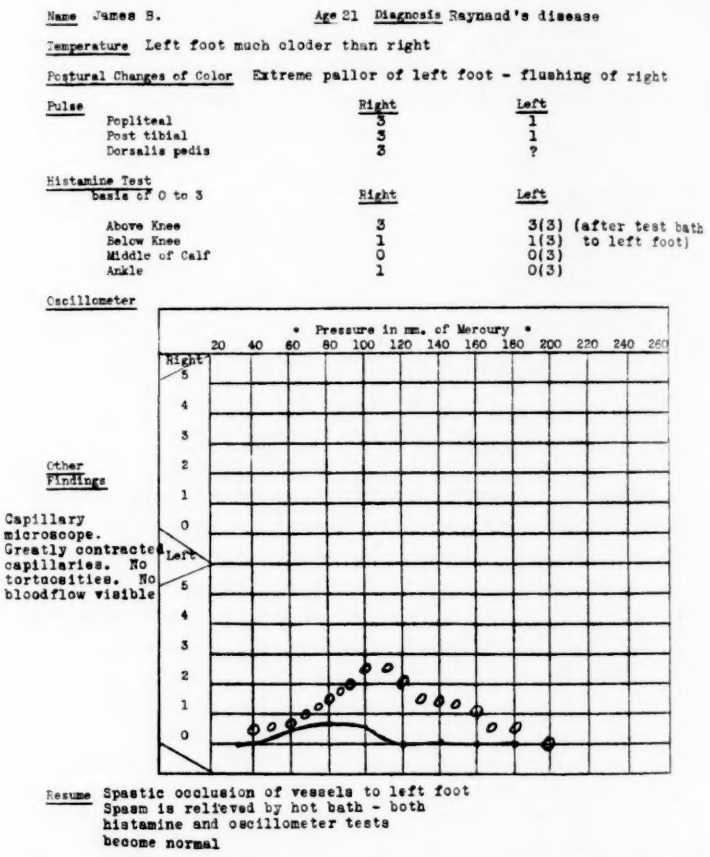

Name James B. Age 21 Diagnosis Raynaud's disease
Temperature Left foot much colder than right
Postural Changes of Color Extreme pallor of left foot - flushing of right
Pulse
Right
Left
Popliteal 3 1
Post tibial 3 1
Dorsalis pedis 3 ?
Histamine Test
basis of 0 to 3
Right
Left
Above Knee 3 3(3) (after test bath
Below Knee 1 1(3) to left foot)
Middle of Calf 0 0(3)
Ankle 1 0(3)
Oscillometer
Pressure in mm. of Mercury
20 40 60 80 100 120 140 160 180 200 220 240 260
Right
Left
5 4 3 2 1 0
Other Findings
Capillary microscope. Greatly contracted capillaries. No tortuosities. No bloodflow visible
Resume Spastic occlusion of vessels to left foot
Spasm is relieved by hot bath - both
histamine and oscillometer tests
become normal

Fig. 8.—Peripheral circulation record. The solid line indicates the oscillations before the test bath; the circle line, those after the test bath.

reaction in the presence of spasm of the cutaneous vessels. For such observations we used: (1) normal persons, before and after immersion in water of 15 C. for five minutes, (2) 1 patient with Raynaud's disease, before and after immersion in water of 40 C. and (3) 2 patients with

polycythemia, who showed an unusual amount of vascular spasm after immersion in cold water.

The histamine reaction is greatly delayed or may be entirely absent during a spasm of cutaneous vessels. Figure 8 shows the conditions in the case of J. B., aged 21, who was suffering from Raynaud's disease. There was a continuous pallor of the left foot when he entered the room from outdoors. The histamine test was negative below the middle of the calf. Correspondingly, the oscillations at the lower third of the calf did not exceed a one-half point. After immersion of the foot in a hot bath (40 C.) for five minutes, the oscillations became definite. At the same time the histamine flares, previously absent, appeared in full strength. Thus a negative histamine reaction may become positive after a hot bath. The importance of such test baths for differentiating organic and spastic arterial occlusions has been emphasized by Babinsky, Froment and Heitz,[19] who recorded the oscillometric changes. The histamine reaction behaves in much the same way, and may thus be used as one of the differential diagnostic measures.

Another interesting observation was made on a young girl who presented symptoms of overcooling, as described by Lewis.[20] After immersion in water at a temperature of 5 C., the leg became hyperemic, the oscillations increased, and the histamine flares became stronger as a result of too cold water, which produced a reactive hyperemia. That such reaction will militate against an intended production of vascular spasm has been emphasized.

It is safe to say that every organic vascular occlusion is superimposed by spasm, but that it is greater in the juvenile than in the senile types. If due only to spasm, the histamine reaction may be made positive by several measures, such as test baths, diathermy, spinal anesthesia or peripheral nerve block. For clinical purposes, an immersion of the limb in water of 40 C. for five minutes should be satisfactory.

The results of the histamine tests carried out on the four groups of patients are shown in the accompanying table.

Results of Histamine Tests

Group	Number of Cases	Reaction to Histamine
1. Normal	50	Prompt
2. Organic occlusions	25	Negative
3. Early disturbances	20	Frequently negative
4. Spastic occlusions	15	Positive after test bath

19. Babinsky, J.; Froment, J., and Heitz, J.: Des troubles vasomoteurs et thermiques dans les paralysies et les contractions d'ordre reflexes, Ann. de méd. **3**:464, 1916.

20. Lewis, Thomas: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, Heart **15**:7, 1929.

COMMENT

The histamine test is a simple and rapid method for determining the collateral circulation in the extremities. It consists of a sensory axon reflex and is dependent on (1) the available blood that can flow into the dilated vessels, (2) the integrity of the short nerve paths that connect the skin with the cutaneous vessels and (3) the state of contraction of the vessels of the skin. As the second factor can be readily excluded and factor 3 can be eliminated by a test bath or other measures, which will be discussed elsewhere,[21] the reaction serves as a simple orientation, concerning the level of adequate collateral circulation. It does not determine with precision the level of vascular occlusion or the diminution of the vascular pulse, as does the oscillometer. It is more of a functional test, as it is conceivable that large vessels with satisfactory collateral circulation have been completely obliterated, as in arrested thrombo-angiitis obliterans. While the reactive hyperemia could be reproduced with other mechanical or chemical irritants, it seems logical to utilize a powerful vasodilator.

The dosage of histamine should not exceed a total of 1 cc. of a 1 : 1,000 solution. The individual wheal should be produced with 0.1 cc., which permits of the use of ten punctures. In several hundred tests, I have never observed a general reaction from such intradermal wheals.

Introduced as a routine measure for all patients with manifest or suspected peripheral vascular disease, the histamine test may give the following information:

1. In patients with frank gangrene, the lowest level for safe amputation is determined. As pointed out by McKittrick and Root,[18] certain infectious types of diabetic gangrene are due to infection and are not of circulatory origin. By demonstrating the adequate collateral circulation with histamine, I was able to save the legs of three such patients. In most cases of arteriosclerotic gangrene the histamine test points to an amputation above the knee, whereas in cases of Buerger's disease the reaction varies according to the development of the collateral circulation.

2. During the course of treatment, improvement or standstill can be demonstrated by the histamine reaction. Thus, in patients with Buerger's disease, it is not uncommon to find a shifting of the normal response to a lower level following a course of treatment with typhoid vaccine.

3. In a beginning embarrassment of arterial inflow, which is not so uncommon in older arteriosclerotic and diabetic patients, the delay or absence of the histamine reaction around the ankle gives an early

21. de Takats, Geza: The Management of Peripheral Vascular Occlusions, Illinois M. J., to be published.

warning. With proper prophylactic measures, the vascular impairment may never progress to frank gangrene.

4. In cases of vascular spasm, the reaction is negative, but such reactions may be changed by any measure that is known to relieve such spasms.

SUMMARY

With a dilute solution of histamine, intradermal wheals produce a distinct arterial flare. This simple clinical test may be used to determine the presence or inadequacy of the cutaneous collateral circulation. Together with palpable changes in the pulse and the temperature of the skin, it affords an estimate of circulatory efficiency of the extremities, provided a few confusing factors are excluded.

INTESTINAL OXYGENATION IN IDIOPATHIC ULCERATIVE COLITIS

PRELIMINARY REPORT *

JOSEPH FELSEN, M.D.
NEW YORK

Prior to three years ago, the best results obtained in the treatment of patients with nonspecific ulcerative colitis coming under my observation centered about the use of colonic irrigations with strong oxidizing agents. Their possible effect on the tissues, the colonic flora or both was noted in a previous communication.[1] While watching the progress of these cases, it occurred to me that perhaps pure oxygen in amounts sufficient to alter materially the gaseous tension in the intestines might prove more effective and less distressing than the fluid irrigation. The encouraging results obtained by the use of oxygen in idiopathic ulcerative colitis prompted this preliminary report.[1a] A final and detailed account of the laboratory and clinical investigations will be made at a future date. The present study comprises a total of 117 cases including control groups, fairly distributed so as to include all types of the disease. The entire group has been under observation for from three to twenty-eight months. Complete cessation of diarrhea, accurate sigmoidoscopic evidence of disappearance of all ulcers and three year after-period of freedom from recurrence have been adopted as reasonable criteria of a cure. The term cure has therefore been avoided in this report.

DIAGNOSIS

Idiopathic ulcerative colitis as accepted in these studies was determined by the following clinical and laboratory data:

Clinical.—Onset of diarrhea of varying degrees of severity with passage of mucus, blood and pus accompanied by colic and tenesmus; proctoscopic or sigmoidoscopic evidence of colitis; in the acute stage, a boggy, hyperemic mucosa covered with blood or pus, and studded with abscesses and ulcers in various stages of formation or healing; confluent ulcers with a granular intervening mucosa; fibrosis of the intestinal wall with stricture or diffuse narrowing in healing or healed cases.

* Submitted for publication, Jan. 19, 1931.

1. Lynch, J. M., and Felsen, J.: Nonspecific Ulcerative Colitis, Arch. Int. Med. **35**:433 (April)) 1925.

1a. Bainbridge, William Seaman: Ann. Surg. **37**:30[illegible] (March) 1909; New York State J. Med., June, 1908, presents an excellent review of the use of oxygen in medicine and surgery.

Laboratory.—In the bacteriologic studies, the following must be proved negative: (*a*) cultural—*Bacillus typhosus, B. paratyphosus* A and B and *B. dysenteriae;* (*b*) smear—*B. tuberculosis*; (*c*) ova and parasites, including encysted forms.

In the serologic studies, the following tests must be negative, except in cases in which the disease is coexistent and unrelated: (*a*) Wassermann test; (*b*) agglutination studies against *B. typhosus, B. paratyphosus* A and B, *B. dysenteriae* and *B. paradysenteriae* of Castellani. In the last named, nine strains are used against a serum dilution of 1:80.

These laboratory examinations are necessary in order to eliminate specific agents known to be responsible for intestinal ulcers. In addition, the routine work has included general fecal studies (gross, chemical and microscopic) and repeated cultural examination of the flora.

BASIC CONSIDERATIONS

Extensive and prolonged observation of patients afflicted with idiopathic ulcerative colitis leaves certain fundamental impressions with regard to the clinical nature of the disease: 1. There is a mild type of ulcerative colitis which, left to pursue a natural course, terminates in complete recovery. 2. Certain patients with the acute form of the disease partially recover and become free from symptoms even though the ulcers persist. 3. There is a definite tendency toward recurrence. Recurrence usually takes place within three years, and not infrequently periodic examination might have revealed that some of the original ulcers had never healed.

The following physiologic and pathologic elements seem to determine the uncertain clinical course of idiopathic ulcerative colitis: 1. The tendency for some ulcers to heal while others form, may be seen in almost every patient. 2. Acute inflammation of the mucosa is generally synchronous with the most marked external evidence of acute illness, while confluence and spreading of the ulcers up the colon may not be indicated by any change in the general physical condition of the patient. 3. Diarrhea, with or without blood, pus and mucus, may persist as long as a single ulcer remains, or may disappear while ulcers persist in abundance. Patients in the latter group are often erroneously discharged as cured. 4. The factor that determines the presence or absence of diarrhea appears to be involvement of the submucosa with its important nerves, lymphatics and blood vessels. I have never been able to section the intestine of patients who, though having visible ulcers, were free from symptoms, but it is my impression that in these cases extensive fibrosis has practically obliterated the submucosa with its delicate nervous structures and so dulled its normal sensitivity. 5. Sudden pain accompanied by fever is always the result of an intramural abscess,

probably primarily affecting the solitary follicles. The tendency for an intramural abscess is to break through the easiest line of resistance, i. e., a thin muscularis mucosae plus one layer of mucosa into the bowel lumen rather than through one or two thick muscular layers and serosa into the peritoneal cavity. Most intramural abscesses are accompanied by a localized peritonitis long in advance of their spread, so that if perforation does occur, it is generally met by an effective walling-off process outside the serosa.

Idiopathic ulcerative colitis appears to be the result of a breakdown of the normal systemic structure and the local intestinal protective mechanism due to factors as yet unknown, plus a superimposed infection. The general lack of resistance to infection may be seen in patients having recent operative wounds elsewhere on the body. At the height of ulcerative colitis, these patients often show as sluggish a tendency toward the healing of these wounds as in the case of their colonic ulcers. After a number of years of study of intestinal flora in normal and diseased persons, it is my impression that the flora of ulcerative colitis differs from the norm quantitatively rather than qualitatively. Thus, in certain cases of ulcerative colitis, I have found streptococci of the type normally constituting a small minority of colonic inhabitants predominating in pure culture. I have under observation one patient in whose case almost daily cultures for two months have shown a pure enterococcus, with a complete disappearance of *B. coli.* A similar observation has been reported by Herter and Kendall. In another instance, *B. mucosus capsulatus* was recovered in almost pure culture.

OXYGENATION OF THE INTESTINE

The first experiments involving the use of uncombined oxygen were made on normal adult subjects in order to get some idea of the intestinal capacity and the distribution and ultimate disposal of a definite amount of the gas. Castor oil was administered the previous night, and after a copious movement of the bowels in the morning, before breakfast, oxygen was released in the rectum through an ordinary enema tube. It was found that on the average 1 liter was tolerated without discomfort, and roentgenograms taken before and five minutes after the administration of oxygen showed that the gas was distributed throughout the small and the large intestine. This seemed to hold true for either the recumbent or the sitting posture. Serial roentgenograms taken at intervals of an hour showed complete disappearance of the gas before the sixth hour, the film being compared with a control taken just before the use of oxygen was started. The physiologic basis for the disappearance of the oxygen is suggested by the experimental observations of other investigators to the effect that gases pass through the

intestinal wall and in so doing follow the known laws of diffusion. Active diffusion tends to continue until an equilibrium has been established between the intestinal lumen on the one hand and the blood and tissues on the other. The small amount of oxygen normally found in the colon is indicated by Fries' [2] analysis of flatus:

Carbon dioxide	10.3 per cent
Oxygen	0.7 per cent
Methane	29.6 per cent
Nitrogen	29.4 per cent

Diffusion between the intestinal lumen and the blood involves chiefly, perhaps solely, the plasma constituent, as the hemoglobin is almost fully saturated (from 95 to 96 per cent) with oxygen. Wright [3] placed the oxygen tension of arterial blood at 100 mm. and that of venous blood at 40 mm. Howell [4] was of the opinion that in the tissues, oxygen is under little or no pressure, being chemically combined and nondissociable. Boycott [5] found that in rabbits the utilization of oxygen by the cells of the intestinal wall is an important factor in accounting for the disappearance of the gas from the lumen of the intestine. McIver, Redfield and Benedict [6] also determined that when the tension in the intestine is low the breathing of oxygen results in an increased tension within the intestine owing to diffusion from the plasma which is holding large amounts of oxygen in physical solution. Campbell [7] reported a similar increase in tension within the peritoneal cavity.

In the preliminary experiments on patients with ulcerative colitis, small amounts of oxygen were used at first; the amount was then increased slowly, in order to determine the effect on the acutely ulcerated or fibrosed intestinal wall. After a series of trials it was found that the average acutely ill adult with intramural abscesses tolerated, without undue distention, as much as 250 cc. given alternate hours between 8 a. m. and 8 p. m. and, to date, without a single instance of perforation. This routine has been adhered to in nearly all cases. In order to measure the amount of oxygen issuing from any given tank, I made use of an ordinary fermentation or ureometer tube, the closed arm of which is marked off at 10 or 20 cc. by previously filling it

2. Fries, J. H.: Intestinal Gases of Man, Am. J. Physiol. **16**:468, 1906.

3. Wright, S.: Applied Physiology, London, Oxford University Press, 1929, p. 353.

4. Howell, W. H.: Text Book of Physiology, Philadelphia, W. B. Saunders Company, 1927, p. 695.

5. Boycott, A. E.: J. Physiol. **33**:343, 1905-1906.

6. McIver, M. A.; Redfield, A. C., and Benedict, E. B.: Gaseous Exchange Between the Blood and Lumen of the Stomach and Intestines, Am. J. Physiol. **76**:92, 1926.

7. Campbell, J. A.: J. Physiol. **60**:20, 1925.

with corresponding amounts of water. The tube is then filled about two-thirds full, expelling all the air from the closed arm. The outlet tube is then inserted, the oxygen valve opened slightly and the number of bubbles necessary to displace 10 or 20 cc. of water counted. The total necessary to make 250 cc. is then computed. With the ordinary oxygen tank, tubing and bottle, the figure is approximately 20 bubbles per minute for one hour, which represents very nearly the slowest rate at which the oxygen will bubble through the indicator bottle without the use of a special reduction valve.

At first, rectal tubes were inserted from 6 to 8 inches (15 to 20 cm.), but this was later found unnecessary, and the ordinary hard rubber enema tip or small soft rubber catheter was substituted. The latter is especially useful in cases in which the rectum or anus is irritated by ulceration and acid stool, as is usually the case in the acute stage of idiopathic ulcerative colitis. It was deemed best to run the oxygen through the indicator bottle holding water at 40 C. in order that the oxygen might reach the intestine at approximately body temperature (37.6 C., 99.68 F.). This precaution, however, was found unnecessary in the summer. Seven hours of oxygen per day administered every other hour between 8 a. m. and 9 p. m. provided a gaseous content of approximately 1,750 cc., or almost 2 liters. The ultimate disposal of such a large amount of oxygen permeating 8.5 meters of intestine is still a problem. It appears certain, however, that part of it is passed by rectum and part absorbed, much of it being absorbed rapidly. The evidence pointing in this direction is that continued observation of some patients shows that no gas is passed by rectum, yet roentgenograms reveal the disappearance of the oxygen.

Most patients receiving the oxygen during alternate hours show at least moderate distention of the bowel as far as the pyloric sphincter. I have thus far been unable to show that the gas passes the pyloric sphincter into the stomach. In this connection, Dr. Jerome Morley Lynch informs me that he has occasionally observed active belching soon after the injection of air into the rectum.

The earliest clinical results to be noted, after from two to seven days of oxygenation, are a diminution or disappearance of foul odor from the stool, cessation of bleeding, improvement in the patient's general condition and possibly fewer movements of the bowels. The last may not always be evident if the patient passes gas at intervals, as not infrequently a small amount of liquid feces is carried out with it. After one or more weeks, the fecal material becomes more formed or, more properly stated, gradually changes from a liquid to a semisolid or pasty movement of good color. At this point the dosage of oxygen is cut down to four hours a day, then gradually lessened and finally stopped when there is no further sigmoidoscopic evidence of ulceration.

Sometimes a sort of spurious diarrhea persists for a few days after the oxygen has been stopped. This may be due to continued increased tension within the intestine.

The effects of oxygenation appear to be due to influence on (1) the intestinal flora and (2) the intestinal tissue proper. Evidence seems to point to the fact that the maintenance of an increased oxygen tension in the intestine leads to the diminution or elimination of spore-bearing anaerobes, encourages the superficial growth of obligatory or faculative aerobes and favors a homogeneity of intestinal flora. These observations, if correct, have an important bearing on the clinical aspect of idiopathic ulcerative colitis. In the first place, a certain number of the acute cases are toxic, the toxicity appearing to coincide with the presence of spore-bearing anaerobes of the *B. welchii* type in the intestine and disappearing with the liberal use of oxygen and elimination or diminution of these powerful toxin-producing organisms. Secondly, oxygen appears to encourage the superficial growth of bacteria and to favor their discharge into the lumen of the intestine and out of the intestine in the form of pus. Evidence pointing to this is that thus far no intramural abscesses have appeared in any patient once the oxygen therapy was well under way. No secondary arthritic complications have occurred. The continued drainage favors healing of the ulcers from the deeper portions upward. It is interesting to note that in the case of one patient having a pure enterococcic flora I found that while at first the organism could be grown aerobically or under partial anaerobiasis, prolonged growth in the incubator under increased oxygen tension seemed to make the organism an obligatory aerobe. The deodorizing effect of oxygenation will perhaps bear repetition at this point. This action may be due to a retardation of intestinal putrefactive processes.

The effect of oxygen on the intestinal tissue proper may consist in part of a diminution or suspension of peristalsis, an observation supported by experimental work on the lower animals. Accurate roentgenographic evidence is not readily obtained because of the difficulty in interpreting pictures made without the use of opaque mixtures. Whether or not the rapid absorption of oxygen by the mucosa stimulates the metabolic activity or increases the natural resistance of the lining cells to injury and infection is open to conjecture. Yet it appears that extensive fibrosis and loss of haustration are not the usual aftermath of intestinal oxygenation. The intestinal wall tends to maintain its normal elasticity and contractility to a great extent, especially in patients oxygenated early in the disease.

In a selected group of patients showing a tendency toward a prevailing streptococcic flora in the fecal discharge, autogenous vaccines were used to supplement oxygenation. In a majority of these cases

the organism corresponded to the enterococcus as described by Huntoon and McElroy, growing readily on ordinary laboratory mediums, resistant to heat, fermentative and not producing a green colony on blood agar. In a number of instances, a diplococcus resembling or possibly identical with the organism described by Bargan was isolated on Rosenow's dextrose brain broth, but some difficulty was encountered in making a positive identification because of variations in sugar-fermenting properties. One patient exhibited a secondary renal focus from which was obtained an enterococcus similar in every respect to the organism occurring in almost pure culture in the colon. The use of vaccines was based on their potential aid in preventing complications (arthritic, renal or myocardial) which not infrequently cause the death of a patient whose intestinal ulcers have almost entirely healed. Every patient receiving the vaccine exhibited a local reaction to the intracutaneous test and a local as well as a systemic response to the subcutaneous inoculations.

Results in One Hundred and Seventeen Cases

Method	Number of Cases	Average Duration, Months	Deaths	Improvement or Possible Cure	Follow-Up, Months
Oxygen	40	7	1	39	3-28
Oxygen plus vaccine	10	8	0	10	3-28
Vaccine	10	7½	0	9	3-28
Irrigation	41	11	6	26	None
Untreated	10	6	2	0	None
Carbon dioxide	3	6	0	0	None
Nitrogen	3	8½	0	0	None

In most cases a prominent secondary effect of oxygenation was a marked increase in hemoglobin and the number of erythrocytes. This may have been due, however, to the cessation of continued small hemorrhages.

COMPARISON OF OXYGENATED AND CONTROL GROUPS

The accompanying table summarizes the results obtained in a total of 117 cases, including the various control groups. The cases in which carbon dioxide and nitrogen were used are perhaps of limited value as controls, as great caution was used in the administration of these gases. It is interesting to note that carbon dioxide appeared to stimulate respiration.

SUMMARY

Oxygenation of the intestinal tract has been productive of encouraging results in the treatment of forty patients with idiopathic ulcerative colitis. I have not attempted generalization, but I have made an effort to present a method worthy of further investigation by others.

AGRANULOCYTHEMIA

REPORT OF A CASE WITH COMPLETE ANTEMORTEM AND POST-MORTEM RECORDS *

C. VICTOR RICHARDS, M.D.

BALTIMORE

History.—Mrs. M. B., aged 28, a clerk, who was separated from her husband, complained that she had tired generally for years. The family history revealed that the mother had been invalided by a fall, and that the father had died of heart trouble. The patient's past history showed influenza, pertussis, measles, chickenpox and intermittent fever with an abscess under the chin. Several teeth had been filled, none of which was abscessed. She had been subject to tonsillitis, and a tonsillectomy had been performed three years before admission to the hospital. She had had slight colds and, ten years before, one attack of hemoptysis. During the past spring she had had a queer, dull, occipital ache, which had been constant for one week (she worked under electric light all day). On exercise and at other times, she had been faint, dizzy and short of breath. The pulse had been rapid. She had had night sweats for one month, and had usually felt sleepy. There had been a slight pulsation in the neck. The lungs were supposed to have been tuberculous, but tubercle bacilli had not been found in the sputum. There had been a loss of weight in 1916, and she had been placed in a sanatorium for one year.

The patient had been troubled with anorexia, but there had been no constipation, gas, eructation of acid or jaundice, and only an occasional feeling of fulness. Menstruation had started at the age of 13; the periods, which had been irregular for one year, then regular, lasted for one or two days and were not accompanied by pain. Once recently, the menses had been profuse and dark. There was a genital discharge, but no sore. There had been no urinary symptoms or pregnancies.

The patient had habitually taken considerable tea or coffee and toast late at night, and the diet had not been well balanced.

On admission the patient said that she had felt worse one year ago than she did then.

Examination.—The patient's appearance was slightly suggestive of an endocrine disturbance, for she had mild hypertrichosis and large facial bones, and she was short; her walk and dress were quasi-masculine.

Examination of the eyes showed that the pupils reacted normally to light and in accommodation. Hearing by air and by bone conduction in the right ear was 25, and in the left ear, 15. There was equal conduction from the center of the head. The mouth, the teeth and the gums were normal in appearance.

Examination of the thorax from the back showed that tactile fremitus was greater on the right side, with a higher percussion note and more distinct breath sounds. Examination from the front showed that whispered sounds were more distinct in the upper right side, and that the percussion note was higher. Voice sounds were transmitted readily, and expiration lagged slightly on the right. Râles were not present in the apexes. There was no deviation or pulsation of

* Submitted for publication, Feb. 16, 1931.

the bronchus. The isthmus of the thyroid gland was palpable. The breasts were equal and pendulous, without lumps, retraction or discharge. Examination of the heart showed good muscular and valvular sound, the aortic and pulmonic being equal. Taken on the left arm, the blood pressure was 130 systolic and 90 diastolic; on the right leg, it was 150 systolic and 100 diastolic. The pulse rate was 84 and regular. The temperature was 99 F.

The pores of the skin were large; the nails were well formed and not particularly brittle; the hair was thick, curly and profuse on the head, and of normal feminine distribution over the body.

The right kidney was not felt. There was pain on pressure of the last rib on the right. Stiller's sign was negative. There was a scar in the region of the appendix, and mild tenderness over the area of the gallbladder. The edge of the liver was not felt. There was a firm, resistant mass in the upper part of the epigastrium to the right of the scar, which felt as if it might be due to cecal stasis and distention. Pelvic examination showed the tubes and the ovaries to be palpable and normal. The uterus, which inclined toward the right, was of normal size.

Examination of the central nervous system showed that the reflexes were equal and active, except that the left biceps reflex was absent. Romberg's sign was not present. Vision was good, and the sensorium was not abnormal.

The Wassermann reaction of the blood was negative. Neither poikilocytosis nor anisocytosis was present. Examination of the blood showed: hemoglobin, 85 per cent; white blood count, normal, with 72 per cent polymorphonuclears, 17 per cent small lymphocytes, 4 per cent large lymphocytes, 6 per cent basophils and 1 per cent eosinophils. Urinalysis revealed albumin, no sugar and numerous epithelial cells.

Beginning on June 18, 1926, an iron preparation was administered intramuscularly over a period of two months. Nonsurgical drainage of the gallbladder was instituted. Analysis of the gastric contents showed: free acid, 11; combined acid, 8, and total acid, 19, as a general average over a period of five drains. The "B" bile occasionally showed bile salt crystals, an occasional group of pus cells, some mucus and at one time a pure growth of Streptococcus albus. Cholecystitis was excluded on these findings. Visualization of the gallbladder by the oral method disclosed a well formed gallbladder, with good density, which opened within five hours after a fat meal. It functioned normally.

The diagnostic impression was: fatigue with irregular gastric hypo-acidity superimposed on a mild dysfunction of endocrine origin.

Course.—Tonic doses of thyroid extract, increased exercise and elimination were ordered by way of treatment. The patient was not seen for one year, during which time she felt quite well. She lost 5 or 10 pounds (2.3 or 4.5 Kg.), and the pulse never reached over 80.

On March 8, 1929, the patient was confined to bed with sinusitis and acute bronchitis, accompanied by generalized aching and sweating. She responded to the usual remedies. Three days later the right antrum of Highmore was drained. Severe swelling on the following day was succeeded by improvement on the day after that. On March 14, the patient was extremely weak. A bright red line extended above and below along the gingival border. On the 15th the temperature was 106 F. The mucous membrane of the throat was highly injected, and the cervical glands were tender and enlarged. There was no jaundice, the spleen was not palpable, the area of the gallbladder was tender, and the calf of the right leg was very tender. On March 16, the patient was taken to the hospital in an ambulance. She breathed with difficulty, as the pharynx and larynx were swollen;

however, respiration was less difficult with the head elevated. The breath was extremely foul. The mucous membrane of the nose was congested, with resulting obstruction to the nasal breathing. The tongue was edematous and coated. The teeth were in fair condition. The gums were coated with a gray exudate; they were edematous, and there was some ulceration of the gingival margins. The glands at the angle of the jaw were enlarged and extremely tender and painful, but there were no fluctuant masses. The thorax, the abdomen and the extremities were normal, except that on pressure the muscles of the left thigh and those of the right calf were very tender.

The diagnostic impression was: acute sinusitis of the right antrum; Vincent's angina of the mouth and throat, and a possible septicemia (Dr. V. H. Norwood).

On March 17, cultures taken from the nose and throat showed staphylococcus; the smears were negative for diphtheria bacillus and the organisms of Vincent's angina. On the 18th cultures from the nose, the pharynx and the epiglottis were negative for diphtheria bacillus, but direct smears from the epiglottis showed the organisms of Vincent's angina. Cultures of the blood on March 16 did not show any growth, but those of the heart's blood at autopsy on March 21 showed Streptococcus viridans.

The Wassermann reaction of the blood was negative. The white blood count on the 16th was 2,100; on the 17th, 900, and on the 18th and 19th, 400. On the 18th, the red blood count was 4,440,000, and the hemoglobin, 70. On March 17 and 18, respectively, the differential count was: neutrophils, 8 and 4 per cent; small mononuclears, 80 and 74 per cent, and transitionals, 12 and 20 per cent. On the 17th, smears showed a considerable increase in platelets, but no anisocytes, poikilocytes or parasites. Urinalysis on March 17 showed: specific gravity, 1.025; acid; sugar, 0; albumin, +; acetone, 0; a few white cells, and a few hyaline casts.

On admission the patient's temperature was 104 F. On the following day her condition was essentially unchanged, but the temperature had risen to 105 F. There seemed to be a slight, definite superficial ulceration of the left anterior pillar, which was covered by a whitish exudate. The patient was given 10,000 units of diphtheria antitoxin intravenously and a transfusion of 500 cc. of citrated blood, to which there was no reaction. The impression of one consultant follows: "1. The history is one of acute sinusitis with drainage. 2. The explanation for the acute infection with high fever should be cleared up by laboratory studies. 3. Vincent's stomatitis is apparently present with some suggestion of exudate on the soft palate. 4. The condition may be laryngeal diphtheria. 5. The leukopenia suggests the possibility of agranulocytic angina. 6. Venous thrombosis in the legs must be watched for; the patient may have actual arthritis."

The impression of a second consultant was: "There is a possibility of laryngeal diphtheria rather than agranulocytic angina because: (1) the involvement of the buccal mucosa is slight; (2) the major part of the lesion is in the upper respiratory tract, probably at the larynx; the patient has a moist rattle, coughs frequently and expectorates large quantities of mucus, and (3) the exudate on the uvula and the left anterior pillar suggests diphtheria."

On March 18, the patient was weaker; her temperature had risen to 106 F., and she was irrational most of the time. She was again given 10,000 units of diphtheria antitoxin intravenously and a transfusion of 500 cc. of citrated blood, without reaction. A third consultant was able to add nothing to the former opinions and findings; his impression was that the entire clinical picture with the blood counts seemed to represent "agranulocytosis." He reported that the pulmonary edema was more pronounced, and that jaundice had appeared.

The patient was irrational throughout the night of March 19. An area of progressive gangrene appeared on the larynx and pharynx, and she died at 10:45 a. m.

Autopsy.—Autopsy was performed by Dr. V. H. Norwood on March 19, at 1 p. m. The body was that of a well developed and well nourished white woman. Rigor mortis was not present. Livid, mottled congestion was present over the trunk, the face, the back and the legs, and a fine icteroid tint over the skin and conjunctiva. The skin was otherwise clear, presenting no ulceration and no evidence of petechiae. The marks of the intravenous injections showed in both cubital fossae. The head was symmetrical, the hair profuse and normal. Examination of the eyes showed the pupils to be equal and regular, with no abnormality except the icteric tint already mentioned. The nose was of normal configuration; the right side showed a small amount of purulent exudate. The ears were normal on external examination. The mouth showed a small amount of grayish exudate about the margin of the tongue, which was coated with a gray membrane. On the left side of the pharynx over the posterior pharyngeal wall was a black, gangrenous patch, measuring about 5 cm. in diameter. There was some superficial ulceration on the anterior pillars of both sides.

Examination of the neck showed that the trachea was in the midline, and that the thyroid was of normal consistency. There was definite enlargement of the glands in the angle of the jaw. These felt firmly fixed to the surrounding tissue. The posterior cervical glands were normal, and there was no enlargement of those in other locations. Examination of the trunk showed nothing abnormal. The abdomen was normal, with a well healed scar in the lower right rectus region. The arms showed nothing remarkable, but the skin of the legs showed the peculiar mottling that has been mentioned. The lower part of the right leg was considerably larger than that of the left; the midcalf measured 35 cm., while that of the left measured 30 cm. There was no pitting edema of the extremities.

The external genitals were of normal configuration, without scarring or ulceration. The breasts were normal, without masses and discharge or secretion from the nipples.

The body was opened by the usual transverse and longitudinal incision. When the peritoneal cavity was opened, the large intestines were found to be markedly distended with gas, but the peritoneal surfaces were smooth and glistening, and no free fluid or exudate was seen. The omentum was firmly bound to the anterior abdominal wall at the site of the old scar. The organs occupied essentially normal positions. The edge of the liver reached the costal margin, its dome extended to the third interspace on the right and to the fifth rib on the left. The gallbladder and pyloric region felt normal. The pelvis was apparently free from inflammatory change. In the thoracic cavity both pleural cavities were entirely free from adhesions, exudate or evidence of acute inflammation. The lungs were normal in appearance.

The pericardial cavity contained a normal amount of clear fluid; both ventricles were firmly contracted. The heart weighed 280 Gm. The tricuspid valve measured 13 cm., the pulmonic, 7 cm.; the mitral, 10.5 cm.; the aortic, 7 cm.; the aorta, 6 cm.; the right ventricle, 5 mm., and the left ventricle, 15 mm. Both ventricles showed good tone. There was a normal amount of pericardial fat and no scarring. On opening the auricles neither thickening, thrombi or hemorrhages were visible. All of the valves were soft, delicate and normal and without evidence of endocardial inflammation. The muscle of the heart was dull pink and did not show hemorrhage or gross evidence of degeneration. The aorta was not dilated, but in the first part of the arch were numerous small atheromatous

plaques. The ductus arteriosus and foramen ovale were not patent. A culture was taken of the heart's blood.

The left lung showed a smooth, glistening pleura. The posterior half of the lower lobe appeared atelectatic, apparently a postmortem change. No area of consolidation could be felt externally. The large bronchi appeared to be normal. There were some glands near the hilus, measuring about 1 cm. in diameter, which were deeply pigmented and contained numerous, translucent, yellowish, almost fatty areas that did not particularly suggest tuberculous change. The bronchi themselves showed slight congestion of the mucous membrane, although this was not remarkable. No exudate was present in any of the bronchi. On section, the tissue of the lung contained air everywhere, except in the congested atelectatic areas that have been described. There was nothing about the gross appearance to suggest pneumonic consolidation or gross tuberculous scarring. Externally, the right lung appeared just like the left. The same atelectasis of the posterior half of the lower lobe was seen, evidently, here also, a postmortem change. Otherwise, the lung contained air everywhere. Evidence of old tuberculous scarring in the apexes was strikingly absent. The large bronchi presented the same picture, and there was similar bronchial change. On section, there was nothing remarkable to be seen.

The spleen was of about normal size; it weighed 180 Gm., and the capsule was soft and delicate. There were a few old, delicate adhesions. On section, the pulp was uniformly firm and deep red, and the fibrous trabeculae were well developed. The malpighian corpuscles were prominent and of normal appearance. Several small, whitish nodules, suggesting old tubercles, were seen in the pulp.

The small intestines were not dilated and, externally, were normal in appearance. The cecum was free from adhesions. There was an old scar at the site of the appendix, which had evidently been removed at operation. No abnormalities were found externally at any point. The mucous membrane was normal, and there was no ulceration. The stomach was small and firmly contracted. On opening, it contained about 200 cc. of brownish fluid, having the appearance of old blood; the mucous membrane, however, was normal, showing no ulceration, exudate or evidence of inflammatory change. There was a rather extensive petechial hemorrhage, such as is often seen at postmortem examination. The pylorus was normal, without scarring or ulceration. The duodenum was normal throughout its length. The ampulla of Vater was easily found, and bile flowed freely on pressure of the gallbladder.

The liver weighed 2,060 Gm. and showed a remarkably well developed quadrate lobe. Its deep purple suggested congestion. It measured 26 by 21 by 9 cm. On section, the architecture appeared normal. The central veins were easily recognized, and there was irregular congestion throughout the tissue. There were numerous light yellow areas, suggesting extensive but irregular fatty degeneration. The organ had a dull appearance, suggesting toxic or cloudy swelling. The actual details of the lobules were less prominent than usual; otherwise the liver showed nothing abnormal.

The gallbladder was thin-walled, delicate and entirely free from adhesions. It contained about 1½ ounces of thin yellowish bile. The mucous membrane was normal, and no stones were found. The rectum showed a normal mucous membrane, free from inflammation and evidence of gangrene. The pancreas measured 19 cm. in length, and weighed 110 Gm. Its architecture and general appearance were normal, and it was firm. The suprarenals were normal in size and consistency on gross and microscopic examination.

The left kidney weighed 140 Gm. and measured 12 by 6 by 3 cm.; the right kidney weighed 180 Gm. and measured 12 by 6 by 3.5 cm. The capsule stripped freely from the left kidney, leaving a smooth surface, free from scarring and hemorrhages. On section, the cortex was of normal thickness and appearance. The striations were normal, and the glomeruli were easily visible. There were no scars or areas of inflammation or degeneration, and no dilatation of the pelvis. The mucous membrane of the pelvis showed small pinhead-sized hemorrhages. The ureter did not show evidence of dilatation, and it was normal throughout its length. The upper pole of the right kidney was surrounded by a small cystic area in the fat which was filled with yellowish-green fluid containing some fibrin. There was nothing about the appearance of this to suggest an acute or pyogenic inflammation. The pelvis on this side was similar to that on the left. The ureter was likewise normal throughout its length.

The bladder contained about 300 cc. of dark brown concentrated urine. Its mucous membrane was normal, but there was some congestion about the trigone. The ureteral orifices were normal and easily admitted a probe. The vaginal mucous membrane was also normal; the cervix was rather soft. Several small black spots, slightly suggestive of gangrene, were found just inside the external os. These were taken for section.

The uterus itself was boggy, but otherwise normal. On section, the endometrium appeared normal. The tubes were soft and delicate, with patent extremities; they were free from adhesions and inflammatory change. The ovaries were normal, the right being larger than the left, measuring 4.5 by 2 by 2 cm. and containing a comparatively fresh corpus luteum.

The organs of the neck were removed as completely as possible without interfering with the large arteries of the neck. The thyroid gland was of normal size and appearance. On section, the normal amount of colloid was present, and there were no adenomas. The esophagus was normal as far anteriorly as the upper margin of the thyroid cartilage. Part of the lateral pharyngeal wall was removed; this was deeply injected and showed an ulcerated lesion which was covered with a necrotic grayish-green membrane. The ulceration was apparently superficial. The entire larynx showed an interesting change. The epiglottis, both arytenoid cartilages and the entire larynx as far as the true vocal cords were edematous and covered by a greenish-black, necrotic membrane which extended over the anterior surface of the epiglottis and forward to the base of the tongue. The lingual surface of the epiglottis was deeply injected, but there was no active necrosis. The margin of this gangrenous area was prominently outlined and was extremely hyperemic. Below and to the left of the vocal cord the trachea was normal. The base of the tongue showed marked hyperemia and hyperplasia of the lymph follicles.

The muscle of the calf of the right leg just inside the gastrocnemius was of normal appearance. The psoas was swollen and extremely firm. Sections were removed from this muscle which showed the tissue to be edematous, with a diffuse hemorrhagic change throughout. Small branches of the veins distributed throughout this muscle showed definite thrombosis. Venous thrombosis probably explained the extreme tenderness that the patient had suffered in this region. Sections of bone marrow were removed from the right femur. Grossly, these were not particularly abnormal, being moderately red and not extremely fat. Sections of the costal cartilage were also taken. Sections were not taken from the brain and spinal cord.

The provisional anatomic diagnosis was: (1) gangrene of the larynx and the pharynx; this anatomic condition taken with the clinical blood findings justified

the consideration of this condition as one of agranulocytic angina; (2) operative removal of the appendix, and (3) thrombosis of the veins of the right leg.

Microscopic Examination.—The muscle of the heart was well preserved, without recognizable scarring or inflammatory change. The arterioles did not show sclerotic change. The endocardial and pericardial surfaces were normal. In places the alveoli of the lungs were dilated and thin-walled, suggesting an emphysematous condition, while in other places they were collapsed. The appearance suggested a mechanical distortion, since no scarring or inflammatory changes were seen. A few red cells were seen scattered in the alveoli and bronchi, but pneumonic exudate was not found. A gland from the hilus of the lung showed a large caseous area, enclosed by a fibrous zone in which numerous tuberculous giant cells were seen. There was considerable fibrosis and pigmentation of the remaining lymphoid tissue.

The architecture of the liver was normal. The cells were not swollen, but the cytoplasm was granular and cloudy. Areas of necrosis or inflammation were not seen. In the tissue immediately beneath the gallbladder, there was slight fatty degeneration of the cells about the portal canal. Fatty changes were not seen elsewhere. There was slight lymphocytic infiltration of the areolar tissue beneath the gallbladder. The wall of the gallbladder was not thickened or infiltrated. Its mucous membrane was delicate, but most of the epithelium was eroded, probably due to postmortem autolysis.

The sinuses of the spleen were engorged with blood, which at many points appeared to have broken through into the pulp spaces, giving an irregularly hemorrhagic appearance. There were few pulp cells, most of them large, with large lobulated nuclei, but a small number of lymphocytes were seen. The malpighian bodies were small, with a reduced number of lymphocytes. In the center, many showed a granular deposit of eosin-stained material, similar in appearance to coagulated protein material, which, however, did not have the appearance of a cellular necrosis. The arterioles showed neither abnormal fibrosis nor degenerative changes. The glandular tissue of the pancreas was well preserved and of normal arrangement. The islets of Langerhans were normal; no necroses were seen.

The structure of the salivary glands was normal. The tissues were well preserved and without degenerative changes. The suprarenal glands were badly torn in removal, but the cellular structure appeared normal. The glomerular zone showed extensive lipoid change, but the remaining cortical cells did not. No abnormalities were seen.

The muscular tissue of the uterus was normal and without cellular infiltration. On the cervix at one point there was slight superficial erosion of the epithelium. There was no destruction of the underlying tissue and no cellular infiltration of the tissue. The appearance of the ovary was normal. Many normal graafian follicles were seen. The structure of the kidney was well preserved. Several fibrosed glomeruli were seen, but otherwise the structures were normal. The arteries did not show thickening.

Section of the pharyngeal wall showed the central necrotic area to be completely degenerated into a granular mass supported by a network of fibrin. The margin of the necrotic area contained many dilated capillaries. Surrounding it, also, was a zone of sparse cellular infiltration. These cells consisted chiefly of mononuclears, evenly divided between lymphocytes and plasma cells. A small percentage of polymorphonuclear cells was also seen. The infiltration extended a short distance between the underlying bundles of muscle. The tonsil showed relatively little evidence of chronic infection in its crypts, but the lymphocytes were rather reduced in numbers. Several small necrotic foci were seen. The germinal

centers presented an appearance similar to that seen in the malpighian bodies of the spleen.

Sections taken from the gastrocnemius muscle showed the muscular bundles to be widely separated by an apparent edema. The muscle itself was extensively degenerated, in most places showing no cross-striations, and in many others showing complete degeneration into irregular hyaline masses. There was extensive extravasation of blood through the muscular tissue. In many places the empty muscle sheath was seen without evidence of regeneration. There were a few mononuclear cells, but the inflammatory infiltration was slight. In these sections, the veins showed some masses of fibrin which completely occluded the lumen.

The bone marrow showed an approximately normal amount of fat. In the marrow of both the long bones and of the ribs, evidence of the formation of red cells was evident, with many megaloblasts and erythroblasts. Megakaryocytes were also numerous. A few scattered polymorphonuclear leukocytes were seen, but none of the usual immature cells and myeloblasts. The marrow was apparently normal with regard to the formation of red cells, with an almost complete disappearance of its leukocytic elements.

The anatomic diagnosis was: (1) gangrene of the larynx and the pharynx; (2) necrosis of the right gastrocnemius muscle secondary to venous thrombosis; (3) old tuberculous scars of the glands at the hilus of the lung, and (4) operative removal of the appendix.

The clinical findings and postmortem examination justified a diagnosis of "agranulocytic angina of Schultze."

The consultants in this case were Dr. Futcher, Dr. Moore and Dr. Hamburger; the laryngologist was Dr. M. Leroy Lumpkin.

THE DEXTROSE LEVEL OF THE ARTERIAL AND VENOUS BLOOD IN ARTHRITIS *

ROBERT M. STECHER, M.D.
AND
HAROLD J. JEGHERS, B.S.
Crile Scholar
CLEVELAND

Decreased dextrose tolerance or delayed removal of sugar from the blood in patients with arthritis was first noted by Pemberton and Foster in 1920.[1] This finding has since been corroborated by some workers and denied by others, resulting in confusion of opinion. With the development of a satisfactory method for the determination of sugar requiring only 0.025 cc. of blood and easily applicable to arterial blood by Jeghers and Myers,[2] it seemed desirable to study the problem anew and to see if the relation of the sugar levels of the arterial and venous blood would shed new light on the subject.

THE LITERATURE

No attempt will be made to review the literature exhaustively. In Pemberton and Foster's [1] series of 400 cases in the Army, the average level in 18 patients with severe arthritis while fasting was 0.113 per cent, which during the dextrose tolerance test for the same series rose to an average high point of 0.189 per cent. In three of these cases the level was over 0.250 per cent at the end of the half-hour or hour periods. In 26 per cent of persons convalescent from arthritis they considered the sugar tolerance to be abnormal. In general, the severity of the disturbance in sugar tolerance seemed to parallel the severity of the disease, but this was by no means constant. They also noted marked improvement in dextrose tolerance after removal of foci of infection. Fletcher [3] observed 100 cases of nonpurulent arthritis from

* Submitted for publication, March 2, 1931.

* From the Departments of Medicine and Biochemistry of the School of Medicine of Western Reserve University, City Hospital.

1. Pemberton and Foster: Studies on Arthritis in the Army Based on Four Hundred Cases; Roentgen-Ray Evidences, Clinical Consideration, Treatment, Summary, Conclusions and Clinical Abstracts of Cases Studied, Arch. Int. Med. **25**:241 (April) 1920.

2. Jeghers and Myers: A Reduction in the Amount of Blood Required for the Folin Micro Blood Sugar Method, J. Lab. & Clin. Med. **15**:982, 1930.

3. Fletcher: The Dietetic Treatment of Chronic Arthritis and Its Relationship to the Sugar Tolerance, Arch. Int. Med. **30**:106 (July) 1922.

the standpoint of dextrose tolerance and improvement with a diet low in carbohydrate. Considering the glycemic level three hours after ingestion of the test meal, he found that in 24 per cent of the cases it was below 0.140 mg. per hundred cubic centimeters; that in 56 per cent it was from 0.14 to 0.20 mg. per hundred cubic centimeters, and that in 20 per cent it was over 0.30 mg. per hundred cubic centimeters. Hench [4] studied 35 cases, in 23, or 65 per cent, of which the dextrose tolerance was abnormal, judged by a rise above 0.160 mg. per hundred cubic centimeters or by a failure to fall below 0.100 mg. per hundred cubic centimeters in two hours. Pringle and Miller [5] found a lowered dextrose tolerance in a large proportion of cases of arthritis and muscular fibrositis, which was roughly proportional to the activity of the arthritis, and which improved with convalescence or cure, especially after the removal of septic foci. Olmsted and Gay [6] noted no constant association of decreased sugar tolerance in arthritis in a small series. Of 4 patients with chronic arthritis, 2 had a normal, 1 a high, and 1 a subnormal, curve. One with acute arthritis, however, had a curve which was high and sustained. Archer,[7] studying 20 cases of chronic infectious arthritis, concluded that there was no evidence of a decreased sugar tolerance in this group. Of 20 women who had arthritis at the menopause, 14, or 70 per cent, had diminished sugar tolerance. Ten of these 14 women, however, had also obesity or hypertension, or both—conditions that may be associated with decreased sugar tolerance. Nondiabetic alteration of sugar tolerance is by no means confined to arthritis. It has been noted in thyroid disease, furunculosis, obesity and hypertension.

METHOD

The clinical determination of arterial blood sugar has been heretofore considered impracticable because of the difficulty and uncertainty of arterial punctures. Such punctures are also attended with sufficient pain to the patient to make frequent repetition undesirable. Foster [8] demonstrated that the dextrose content of capillary blood obtained by deep puncture of the foot pads of dogs was identical with that of arterial blood. Our observations show that freely flowing capillary

4. Hench: The Systemic Nature of Chronic Infectious Arthritis, Atlantic M. J. **28**:425, 1923.

5. Pringle and Miller: Glucose Tolerance in Chronic Arthritis, Lancet **1**:171, 1923.

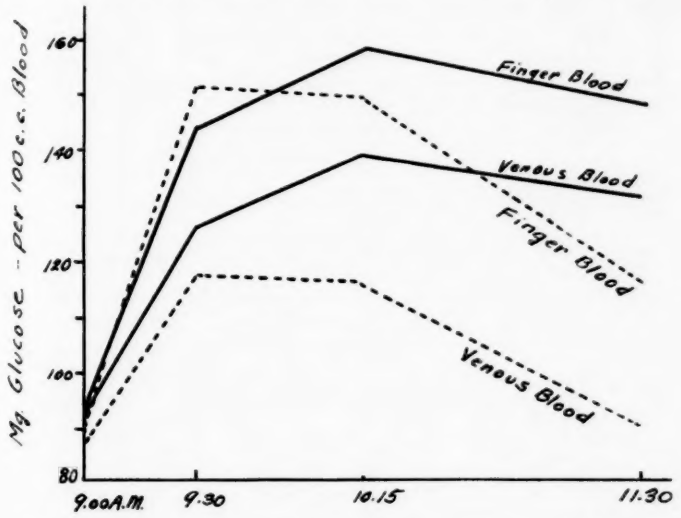
6. Olmsted and Gay: Study of Blood Sugar Curves Following a Standardized Glucose Meal, Arch. Int. Med. **29**:384 (March) 1922.

7. Archer: Sugar Tolerance in Arthritis; Chronic Infectious Arthritis, Arch. Int. Med. **44**:37 (July) and 238 (Aug.) 1929.

8. Foster: Studies on Carbohydrate Metabolism, J. Biol. Chem. **55**:291, 1923.

blood constantly has a higher dextrose level than venous blood, except in the fasting state, when the levels are the same within the limits of error of the determination. Our findings are in every way compatible with his conclusions. The technic of Jeghers and Myers, an adaptation of Folin's micromethod, in which only 0.025 cc. of blood is required, was used. This amount is easily obtained by puncture of a finger. The procedure is briefly as follows:

The patients fast from the previous evening. On the morning of the test, while the patient is still fasting, specimens of the arterial and venous blood are obtained a few minutes before 9 a. m. At 9 a. m., 100 Gm. of dextrose dissolved in water flavored with orange or lemon juice is given orally. Additional specimens of blood



Curves of dextrose tolerance in arthritis. The continuous lines represent averages of fourteen curves in 11 cases of arthritis. The dotted lines represent averages of ten curves in 10 control cases. The subjects fasted from the evening preceding the tests. On the morning of the tests, specimens of blood were taken while the patients were still fasting. At 9 a. m., 100 Gm. of dextrose was given orally, and specimens of blood were taken one-half hour, one and a quarter hours and two and a half hours later. The number of milligrams of dextrose per cubic centimeter of the blood was determined.

are obtained one-half hour, one and a quarter hours and two and a half hours later.

Blood is obtained by a deep puncture of the ball of the finger tip. The first drop of blood flowing out is wiped away, and the second is drawn into a capillary pipet calibrated to 0.025 cc. The blood usually flows without massage of the finger. This 0.025 cc. of blood is immediately expressed into 5 cc. of dilute tungstic acid solution. The venous blood is obtained from the median basilic vein with a

syringe and needle. The needle is then removed from the syringe and the plunger pushed in until a drop of blood appears at the tip of the syringe. This is then drawn up into a capillary pipet to the 0.025 cc. mark and this quantity of blood expressed in dilute tungstic acid. With the assistance of a nurse at the bedside, it is thus usually possible to obtain both samples and to have them precipitated within a minute of each other. Anticoagulants are not necessary.

TABLE 1.—*Dextrose Levels in Arterial and Venous Blood in Arthritis*

Patient	Type of Arthritis	Fasting		½ Hour		1¼ Hours		2½ Hours	
		Finger	Venous	Finger	Venous	Finger	Venous	Finger	Venous
R. W.	Atrophic	96*	99	152	138	207	194	204	188
R. W.	Atrophic	97	96	131	118	173	164	177	163
W. T.	Hypertrophic	88	85	182	165	175	158	160	140
F. N.	Atrophic	87	85	152	132	180	162	158	139
M. L.	Atrophic	102	99	180	162	166	144	155	138
C. W.	Atrophic	103	102	143	119	165	139	155	135
J. P.	Atrophic	92	90	132	116	151	125	153	139
J. H.	Atrophic	83	80	152	137	165	144	148	130
T. E.	Atrophic	101	98	142	118	146	122	156	128
G. H.	Hypertrophic	81	79	147	120	155	134	140	120
J. P.	Atrophic	82	82	118	94	151	119	128	121
G. H.	Hypertrophic	99	97	121	107	136	118	122	112
D. G.	Atrophic	112	110	160	135	138	118	119	95
A. T.	Atrophic	98	96	120	109	132	112	106	90
Average		94	92	144	126	158	139	148	132
Difference between sugar contents of finger and venous blood		2		18		19		16	

* Throughout the table the figures represent milligrams of dextrose per hundred cubic centimeters of blood.

TABLE 2.—*Dextrose Levels in Arterial and Venous Blood in Control Cases*

Patient	Diagnosis	9 a. m.		9:30 a. m.		10:15 a. m.		11:30 a. m.	
		Finger	Venous	Finger	Venous	Finger	Venous	Finger	Venous
C. C.	Tabes dorsalis	90*	91	139	117	168	128	123	103
A. S.	Abscess of the lung	99	99	148	117	179	136	126	106
J. S.	Multiple sclerosis	96	94	134	122	132	112	104	79
J. H.	Chronic bronchitis	94	96	169	131	148	118	112	94
C. P.	Chronic alcoholism	95	95	166	113	149	108	130	93
R. T.	Bronchitis	86	86	153	106	124	99	108	89
E. H.	Emphysema	81	78	129	101	152	115	128	97
E. S.	Carcinoma of bronchus	83	83	143	100	118	90	106	78
M. N.	Chronic alcoholism	84	96	160	136	147	121	112	88
A. V.	Amytrophic lateral sclerosis	85	85	148	116	174	134	113	84
Average		91	88	151	117	149	116	116	91
Difference between sugar contents of finger and venous blood		3		34		33		25	

* Throughout the table the figures represent milligrams of dextrose per hundred cubic centimeters of blood.

Each specimen is then kept in an icebox until the test is completed. The sugar in the supernatant solution after centrifugation is oxidized with alkaline potassium ferrocyanide, and the ferrocyanide produced is measured colorimetrically, a yellow filter being used for the light. The specimens are all analyzed against the same standard.

MATERIAL

Fourteen dextrose tolerance tests of both arterial and venous blood were made on 11 arthritic patients, the results of which are given in table 1. The tests are arranged in the order of the elevation of arterial sugar after two and a half hours.

Every test made has been included, and all show a definite elevation over the normal, save possibly the last two.

The patients were all hospitalized and were kept in bed during the test, but many were otherwise ambulatory. Seven were males and four were females. They varied in age from 17 to 65, and they had suffered from arthritis for from four weeks to ten years. Two cases were classified as hypertrophic, while the others were atrophic. Of the 11 patients 5 (W. T., C. W., G. H., D. G. and A. T.) showed no fever at the time of the test. Six had some fever. Of these, 4 (F. N., J. P., J. H. and T. E.) had definite foci of infection, which were subsequently removed. Two patients with fever (R. W. and M. L.) revealed no definite foci. The latter of these recovered spontaneously, and the other died. The last 2 patients listed in the table were without fever. D. G. had severe atrophic arthritis with marked deformity, but no evidence of an active process. A. T. had had a severe gonorrheal arthritis, which had left her with several ankylosed joints, but she had been free from active arthritis for several months.

Ten patients were chosen from the medical wards as controls. They were selected because of their probably normal sugar metabolism. None had ever shown sugar in the urine. The data on this group are tabulated in table 2, with the diagnoses. The chart was made by plotting the arithmetical averages of the glycemic levels of each group.

RESULTS AND COMMENT

In studying the tables and charts, it must be remembered that the venous blood levels alone are comparable with other series so far published. The rise of the sugar in the venous blood is not as high as has been reported by previous workers, but the continued elevation is marked compared with that in our controls.

In the arthritic patients the level of the venous blood dextrose is much higher, the peak is reached later, and the fall is much slower, than in the controls. On considering the level of the arterial blood sugar it is seen that the rise is a trifle slower and reaches the peak later, and that the fall is much slower, in the arthritic patients than in the controls. The difference between arterial and venous blood sugar levels is very much less in the arthritic patients than is normal. There appears to be a slight delay in the removal of dextrose from the intestines of arthritic patients, indicated by the slightly lower level of dextrose in the arterial blood after thirty minutes, but this delay is less marked than is that of the removal of the dextrose from the blood to the tissues. It is apparent that the amount of dextrose removed by the tissues from the blood in arthritic patients is definitely reduced.

While many observations of venous blood sugar in health and in all manner of diseases have been reported, little is known of the arterial blood sugar. In a resting and fasting state, an equilibrium is reached between the sugar content of the blood and the other sugar storehouses of the body, the muscles and the liver. Little, if any, utilization of sugar is occurring, so we should expect no difference between arterial and venous dextrose. This is found to be the case in the arthritic

patients and in the controls. During a dextrose tolerance test, the equilibrium is disturbed, and absorption of dextrose from the gastro-intestinal tract increases the sugar content of the blood. The dextrose level in the blood depends on the relation between the rate of absorption from the gastro-intestinal tract and the rate of removal from the blood. Both of these mechanisms depend on the efficiency of the circulation and the permeability of the capillaries. The rate of exchange of dextrose from the blood to the tissues may be influenced by the mass of muscle available for storage and the efficiency with which capillary blood is held in contact with it. This efficiency depends to some extent on the surface area of permeable capillaries and the rate of flow of blood through them. The difference between the sugar contents of arterial and venous blood gives us a measure of this efficiency.

Which of these factors seems of most importance in the altered sugar metabolism of arthritic patients? Inadequacy of the general circulation may be eliminated, as circulatory failure seems rare in this type of case, nor was it suspected in any of our patients. The fact that absorption from the stomach was the same as in the controls argues against an explanation on this basis. That reduction of muscle mass might be important is admitted. It happens that the most abnormal curves were obtained in the case of a patient with extreme and generalized atrophy of the muscles (R. W.). The arterial and venous glycemic levels reached the highest points obtained, but the difference between them was not far from the average. The patient had ankylosis of both hips, knees, spine and all the ribs, and marked limitation of motion of all other joints, had a fever constantly, and generalized glandular enlargement, and, at autopsy, showed adhesive pericarditis. Another patient with generalized atrophy (D. G.) had a much lower curve. Generalized atrophy of the muscles was not seen in the other patients.

That some alteration in capillary permeability exists, interfering with the removal of dextrose from the blood, has been suggested by Pemberton.[9] He observed that during the conduction of a test revealing a lowered sugar tolerance there is in most cases a rise in the percentage of saturation of that blood with oxygen. That is to say, the ratio of the oxygen content to the oxygen capacity increases, which means that more oxygen is left unutilized. He further observed that a small difference in the percentage of saturation of the peripheral venous blood with oxygen existed between groups of normal persons and the groups of arthritic patients studied. By direct observations

9. Pemberton: Arthritis and Rheumatoid Conditions: Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929.

of the flow of blood in the capillaries of the nail-bed, Pemberton and his co-workers observed that, in comparison with normal nail-beds, the arthritic ones showed on the whole distinctly less blood in the field, closure or narrowing of many capillaries, irregularity and slowing down of blood flow and often a difference in the amount of blood in the venous, as compared with the arterial, limb of a capillary. They have seen an increase in the number of permeable capillaries, with a better blood flow through them, in arthritic patients following procedures of recognized therapeutic value to the arthritic patient, such as heat, massage, exercise and administration of caffeine and salicylates. Pain and stiffness in the joints, as well as alterations in the peripheral circulation of arthritic patients, demonstrated by pallor and coldness of the extremities, can partially be explained on the basis of subnormal capillary function. This, we believe, best explains the delayed removal of dextrose from the blood in arthritic patients.

SUMMARY

1. A practical method for the determination of arterial dextrose levels is described.

2. Observations of dextrose tolerance tests in arthritic patients and in controls, made on venous and arterial blood, are recorded.

3. Decreased and delayed removal of sugar from the blood of arthritic patients is demonstrated.

4. This seems best explained on the basis of a decreased capillary function in the peripheral circulation.

DETERMINATION OF PLASMA VOLUME

I. THE DYE METHOD *

SAMUEL GRAFF, B.S.
AND
H. T. CLARKE, D.Sc.
NEW YORK

The determination of the total volume of the circulating blood or plasma is assuming increasing importance from both the clinical point of view and that of research (Erlanger,[1] Rowntree, Brown and Roth,[2] Stander [3]). A study of the variation of the blood volume in pregnancy having been projected in this laboratory, it became necessary to investigate the methods for determination of blood volume. This paper deals with the results of the investigation.

The extensive literature on the subject discloses two basically different methods in use: the carbon monoxide method of Haldane and Smith [4] and the dye method of Keith, Rowntree and Geraghty.[5] When using the former method, one must consider myohemoglobin (Whipple [6]), the dependence on environmental temperature (Barcroft et al.[7]), the time lag in saturation of the hemoglobin in the splenic spaces (Barcroft and Barcroft [8]) and the local differences in cell concentration (Lamson and Nagayama [9]). An analysis of the data obtained

* Submitted for publication, Feb. 20, 1931.

* This work was aided by grants from the Chemical Foundation.

* From the Department of Biological Chemistry, Columbia University College of Physicians and Surgeons.

* From a thesis submitted by S. Graff in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Columbia University.

1. Erlanger, Joseph: Physiol. Rev. **1**:177, 1921.

2. Rowntree, L. G.; Brown, G. E., and Roth, G. M.: The Volume of the Blood and Plasma in Health and Disease, Mayo Clinic Monograph, Philadelphia, W. B. Saunders Company, 1929.

3. Stander, H. J.: Medicine **8**:1, 1929.

4. Haldane, J., and Smith, J. L.: J. Physiol. **25**:331, 1899.

5. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

6. Whipple, G. H.: Am. J. Physiol. **26**:685, 1926.

7. Barcroft, J.; Binger, C. A.; Bock, A. V.; Doggart, J. H.; Forbes, H. S.; Harrop, G.; Meakins, J. C., and Redfield, A. C.: Phil. Tr. Roy. Soc., London, s. B., **211**:351, 1922. Barcroft, J.; Meakins, J. C.; Davies, H. W.; Scott, J. M. D., and Fitter, W. J.: ibid. **211**:455, 1922.

8. Barcroft, J., and Barcroft, H.: J. Physiol. **58**:138, 1923.

9. Lamson, P. D., and Nagayama, T.: J. Pharmacol. & Exper. Therap. **15**: 331, 1920.

by the carbon monoxide method fails to inspire confidence, blood volumes ranging from 2.6 per cent (Oerum[10]) to 8.8 per cent (Douglas[11]) of the body weight having been reported. Our choice of the dye method was based on the greater convenience of manipulation as well as on the difficulty of interpretation of data of the carbon monoxide method.

Although many workers accept the dye method for the determination of plasma volume, objection has been raised (Lamson and Nagayama[9]) to the computation of blood volume on the basis of hematocrit readings, no assurance being possible that the cell volume content of any sample is representative of that of the blood throughout the system. We have, therefore, in this paper limited our calculations to those of plasma volume. The question of uniform distribution of the dye throughout the plasma will be discussed in the second paper of this series.

Dawson, Evans and Whipple[12] showed that the use of dry oxalate causes shrinkage of the corpuscles, yielding low results. They recommend the use of 2 cc. of a 1.6 per cent sodium oxalate solution for 10 cc. of the blood of peptonized and heparinized dogs, and suggested that in general the oxalate should be in a solution isotonic with the blood.

We have determined the optimal concentration of potassium oxalate for human blood and found it to lie between 0.9 and 1.1 per cent.

Brilliant vital red, recommended by Dawson, Evans and Whipple proved eminently suitable to our technic. It is nontoxic and nonirritant; it mixes well in the blood stream, and its absorption by the tissues and blood cells is slow.

The effect of hemoglobin on the colorimetric determination of dye in the resulting plasma must also be considered.

With the exception of the statement by Keith, Rowntree and Geraghty[5] that samples could be matched accurately even though slight hemolysis had occurred, reference in the American literature to the effect of hemolysis is conspicuously absent. On the other hand, German workers (Griesbach,[13] Hartwich and May[14]) advocated a spectroscopic examination for hemoglobin, with the rejection of hemolyzed samples. In our preliminary studies the incidence of hemolysis was sufficiently

10. Oerum, H. P. T.: Deutsches Arch. f. klin. Med. **93**:357, 1908.

11. Douglas, C. G.; Haldane, J. S.; Henderson, Yandell; and Schneider, E. C.: Proc. Roy. Soc., London, s. B., **85**:65, 1912.

12. Dawson, A. B.; Evans, H. M., and Whipple, G. H.: Am. J. Physiol. **51**:205 and 232, 1920.

13. Griesbach, W.: Deutsche med. Wchnschr. **2**:1289, 1921.

14. Hartwich, Adolf; and May, Gertrude: Ztschr. f. d. ges. exper. Med. **51**: 497, 1926.

great (60 per cent in certain instances) to disqualify many cases.[15] When hemolysis could be recognized by the eye, no match was possible in the colorimeter; on the other hand, when the samples could be matched, and the calculated plasma volume was low, the spectroscope often revealed the hemoglobin band at 574 millimicrons. Accordingly, our problem was not that of detecting hemolysis for the sake of rejecting the sample, but of determining the dye component in samples contaminated with hemoglobin whenever hemolysis had occurred to even the slightest degree; that is, the amount of one colored substance must be determined in the presence of two others.

TABLE 1.—*Spectroscopic Determinations* *

			5 Cc. Dye Solution 5 Cc. Plasma		5 Cc. Dye Solution 2.5 Cc. Plasma 2.5 Cc. Water		5 Cc. Dye Solution 0.5 Cc. Plasma 4.5 Cc. Water		1 Cc. Dye Solution 9 Cc. Plasma		5 Cc. of 9% Dye Solution 5 Cc. Plasma	
Wave Length, Mμ	Density of 100% Plasma	Density of 2% Dye in Water	Total Density	Net Dye Density × 2	Total Density	Net Dye Density × 2	Total Density	Net Dye Density × 2	Total Density	Net Dye Density × 10	Total Density	Net Dye Density × 0.222
491	0.580	1.891	2.850	2.560	2.690	2.545	2.605	2.576	0.7741	2.531		
499	0.507	1.875	2.803	2.640	2.680	2.562	2.719	2.694	0.7170	2.610		
507	0.435	1.820	2.977	2.760	2.837	2.731	2.862	2.840	0.6709	2.789		
516	0.393	1.706	3.036	2.840	2.958	2.860	2.922	2.902	0.6278	2.738		
526	0.372	1.511	2.926	2.740	2.893	2.800	2.749	2.730	0.6040	2.696		
536	0.388	1.257	2.686	2.490	2.502	2.405	2.560	2.541	0.5913	2.423		
548	0.355	1.001	2.178	2.000	2.101	2.012	1.981	1.963	0.5301	2.101		
560	0.313	0.665	1.162	1.005	1.078	1.000	1.026	1.010	0.3832	1.012	2.387	1.003
574	0.359	0.305	0.636	0.456	0.552	0.462	0.491	0.473	0.3646	0.426	1.175	0.448
590	0.248	0.097	0.283	0.159	0.224	0.162	0.161	0.149	0.2369	0.139	0.481	0.161
606	0.240	0.018	0.156	0.036	0.089	0.029	0.053	0.041	0.2216	0.056	0.209	0.040

* Plasma slightly hemolyzed. Net values calculated to unit cell depth of 5 mm.

Attempts at chemical separation of the dye from blood plasma were fruitless, the plasma proteins and dye behaving alike toward salting-out, precipitation by the heavy metals, and colloidal precipitants. Extraction of the dye with butyl alcohol (which is readily possible with acidified aqueous solutions) also failed, owing to the precipitation of blood proteins and the occlusion therein of some of the dye.

The colloidal character of the dye is indicated by the dependence of its absorption spectrum on the colloidal conditions of its solution, a property also shown in the salt and protein errors of certain indicator

15. While it is generally possible to obtain blood without hemolysis on the first puncture, this has not been proved to be the case with subsequent samples. The tendency toward hemolysis increases with the frequency of bleedings, especially when samples are taken in rapid succession and with limited stasis. The use of a Lindemann needle proved impracticable, owing to coagulation in the cannula.

dyes (Clark [16]). Heilmeyer [17] showed that the absorption spectrum of congo red is shifted by the presence of plasma proteins.

With brilliant vital red, plasma proteins increase the absorption throughout the spectrum, the effect being consistent and independent of plasma and dye concentration within wide limits (table 1). Other

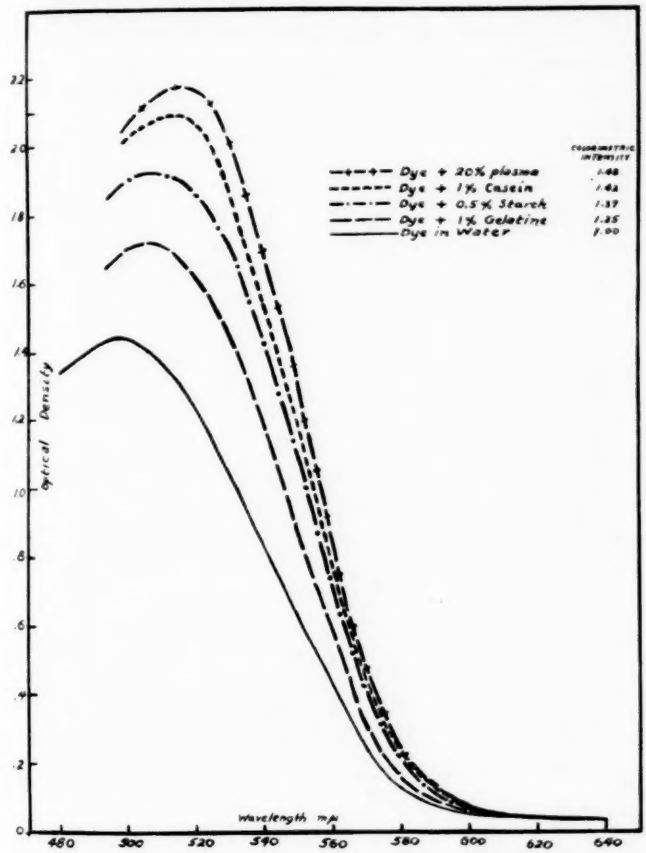


Chart 1.—The effects of certain colloids on the absorption spectrum of brilliant vital red. The dye concentration is constant throughout. Colorimetric intensity is the ratio of observed intensity to that of dye in water, when viewed through a Wratten filter no. 75.

16. Clark, W. M.: The Determination of Hydrogen Ions, Baltimore, Williams & Wilkins Company, 1928.

17. Heilmeyer, L.: Biochem. Ztschr. **212**:430, 1929.

colloidal substances produce the same general effect, each one causing a specific change, independent of the amounts added. The absorption curves obtained in a series of experiments are reproduced in chart 1.

The absorption spectrum of brilliant vital red is, moreover, altered by certain salts.[18] The effects (chart 2) of 1 per cent and 2 per cent sodium chloride, and of 1.042 per cent sodium sulphate (sodium concentration equivalent to that of 1 per cent sodium chloride) are

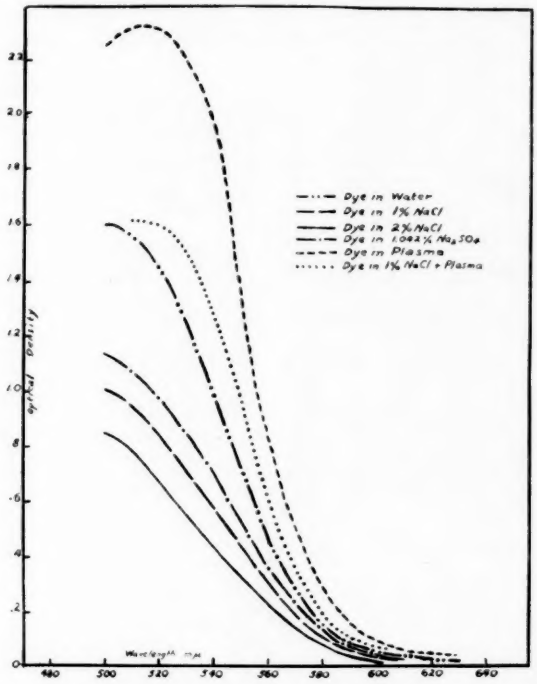


Chart 2.—The effects of certain salts on the absorption spectrum of brilliant vital red.

opposite to those caused by the added colloids. When both plasma and salt are present, these opposed effects partially neutralize each other.

Colorimetric comparison was made when the added colloidal solution had no intrinsic color value. Direct comparison between the

18. Our attention was drawn to this effect of salts by obvious discrepancies between our initial observations and those reported by Smith (footnote 19) who cooperated with us in ascertaining the reasons for the discordance between observations in the two laboratories.

aqueous dye standard and the colloid dye solution was not possible, since the shift of the spectrum corresponds to a qualitative change in color; that is, the two colors appear different to the eye. When a filter (Wratten no. 75) having maximum transmission at the region of maximum absorption of the dye was employed, the two fields could be matched and showed inequalities in intensity corresponding to those obtained with the spectrophotometer.

In order to determine the concentration of the dye in blood plasma, it is thus necessary to use a standard with the same absorption spectrum.

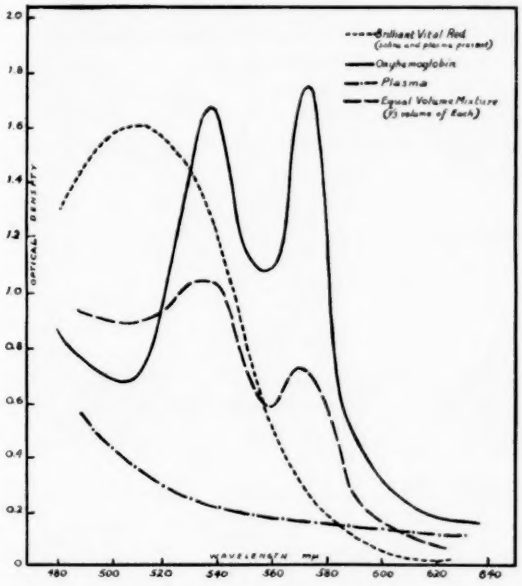


Chart 3.—Absorption spectra of the components of the mixture of brilliant vital red, plasma and oxyhemoglobin.

To prepare this, a small volume of the dye solution as injected might be diluted to a convenient volume with blood plasma, but since it is not feasible to employ the necessarily large quantity of representative plasma, the dilution is made with 0.9 per cent sodium chloride, and a definite volume of the resulting solution is added to a known volume of plasma. Any convenient amount of plasma may be used, since, as was stated, the effect of the protein appears to be dependent only on the nature of the protein, and not on its concentration. The salt content, on the other hand, must be maintained at a uniform level.

The absorption spectra of solutions of brilliant vital red in diluted plasma from hemolyzed samples were determined over the range 476 to 667 millimicrons. Beer's law was found to hold for solutions, in 0.9 per cent sodium chloride, of the dye, oxyhemoglobin and plasma; the spectral transmission curves for these solutions, alone and mixed, are reproduced in chart 3. It will be observed that the curves for the dye and the hemoglobin overlap so that there is no wavelength at which the absorption of dye can be measured without encountering that of oxyhemoglobin. However, the various peaks are so well defined that the composition of any mixture can be calculated from the absorption values at two wavelengths (Smith,[19] Barnard, Monroe and McMichael[20]).

Let A and B represent the observed optical densities of a mixture of the dye and oxyhemoglobin at wavelengths 1 and 2, respectively. Let D_1 and D_2 represent the optical densities of a standard concentration of the dye solution, and Hb_1 and Hb_2 the densities of any convenient standard solution of oxyhemoglobin, at the same wavelengths, respectively. Then

$$\begin{aligned} A &= yHb_1 + xD_1 \\ B &= yHb_2 + xD_2 \end{aligned}$$

and

$$\frac{A - xD_1}{B - xD_2} = \frac{yHb_1}{yHb_2} = k$$

whence

$$x = \frac{A - kB}{D_1 - kD_2}$$

In these equations, x and y represent the concentration of dye and hemoglobin, respectively, in the mixture. The proportion of dye in the mixture, expressed as percentage of the dye standard, is thus given by $100x$.

Hb_1 and Hb_2 are therefore determined with any convenient concentration of oxyhemoglobin, and the value of k is calculated. D_1 and D_2 are computed from observations made on a convenient dilution in salt-plasma solution of the dye solution used for injection. While Hb_1 and Hb_2 are of value only in computing k, which is a constant, characteristic of oxyhemoglobin, D_1 and D_2 must be determined separately for each case; further, D_1 and D_2 are the net dye densities, the standard dye-plasma densities having been corrected for the component plasma density.[21] Wavelength 1 should be chosen at a minimum and wave-

19. Smith, H. P.: J. Exper. Med. **51**:369, 1930.

20. Barnard, Monroe; and McMichael, Paul: Indust. & Engin. Chem. **2**:363, 1930.

21. For example, at wavelength 516, with all values computed on a 5 mm. cell basis mixture of 5 cc. plasma and 5 cc. dye in solution, the density of the mixture was 1.375 and the density of the plasma was 0.250. The plasma had suffered a 50 per cent dilution; therefore, the density of the dye in the 1:2 dilution mixture equals the density of the mixture less one-half the density of the plasma: $1.375 - \frac{1}{2}\ (0.250) = 1.250$.

length 2 at a maximum in the oxyhemoglobin absorption curve. Wavelengths 507.5 millimicrons and 574.0 millimicrons are theoretically ideal, though practically any other combination of wavelengths within the limits 500-520 and 570-580 millimicrons gives good results. Since the absorption of the dye is slight at wavelength 574 millimicrons, the use of very deep cells is necessary with dilute dye solutions. The value of k at these optimum wavelengths, 507.5 and 574.0 millimicrons, was found to be 0.383.

In the foregoing calculations no account is taken of the absorption due to plasma. If the dilution factors of the dyed and undyed samples are the same, and if no hemolysis has occurred in the case of the undyed control sample, the effect of the intrinsic absorption of the plasma can be balanced by placing the control sample in the solvent chamber of the Schulz cell. This effect is relatively small, but not negligible, the general absorption increasing toward the blue end of the spectrum. If the dilutions of plasma are not the same, as in the general case, the absolute optical density values at the selected wavelengths must be determined on the control sample and allowance made for the plasma component in the dye sample. This involves the following modification of the formula:

$$x = \frac{\left[A - \frac{C_1 R_1}{C_2} \right] - k \left[B - \frac{C_1 R_2}{C_2} \right]}{D_1 - D_2}$$

in which R_1 and R_2 represent the absorption values of the control sample at wavelengths 1 and 2, respectively, and C_1 and C_2 the concentrations of plasma in the control sample and the dyed sample, respectively. The method of computing C_1 and C_2 is discussed in footnote 24.

If the control plasma is hemolyzed, the true plasma component must be determined before substituting in the foregoing equation. This procedure, however, will be necessary only when the control plasma contains sufficient hemoglobin to give it a noticeably red color.

Examination of numerous samples of plasma at wavelengths 560 (3) and 574 millimicrons (2) has indicated the normal value of the expression $\frac{P_3}{P_2} = s = 1.06$ (chart 4), in which P_2 and P_3 represent the optical densities of the plasma at wavelengths 2 and 3, respectively. In hemoglobin the corresponding ratio is $\frac{Hb_3}{Hb_2} = t = 0.603$.

The proportion of plasma (Z) in the hemolyzed control, referred to the standard plasma solution (P_3, P_2) as unity, is thus given by the expression $\left[z = \frac{M_3 - TM_2}{P_2 (S - T)} = \frac{M_3 - 0.603 M_2}{0.457 P_2} \right]$ for wavelengths 560 and 574 millimicrons, respectively, in which M_2 and M_3 represent the optical densities of the hemolyzed control plasma at wavelengths 2 and 3, respectively. Measurements at wavelengths 560 and 574 millimicrons are ideal for this calculation. The true control plasma densities zP_1

and zP_2 must then be substituted for R_1 and R_2 when the foregoing computations are necessary, giving us a final form:

$$x = \frac{\left[A - \frac{C_1 z P_1}{C_2} \right] - k \left[B - \frac{C_1 z P_2}{C_2} \right]}{D_1 - k D_2}$$

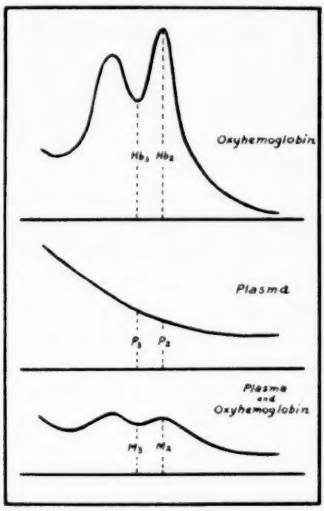


Chart 4.—Absorption spectra of oxyhemoglobin and of plasma.

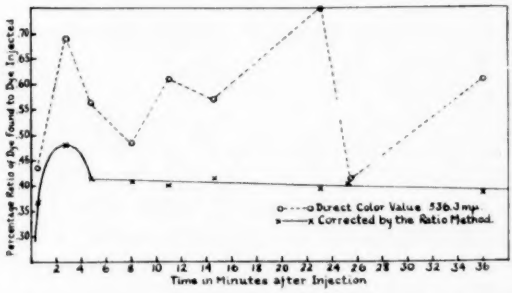


Chart 5.—Comparison of dye readings obtained by colorimeter and by spectrophotometer.

All density values are determined with water in the solvent chamber, and all densities are referred to a standard cell depth.

The use of the foregoing principles is illustrated in chart 5. The irregular curve depicts the values obtained on direct colorimetric com-

parison of the various members of a series of samples withdrawn from a subject at intervals after injection of the dye; the smooth curve depicts the correct values obtained on the same samples with the use of the spectrophotometer.

Numerous attempts were made to adapt an analogous principle to the use of the colorimeter. This process, which is theoretically feasible, nevertheless failed because of the impracticability of obtaining suitable monochromatic illumination of sufficient intensity. Attempts to compare intensities of color through optical filters were fruitless, as the transmission bands of all available filters were so wide as to render impossible a true match in color. The same obstacle prevented the successful employment of the Pulfrich "gradation photometer" recently developed by Zeiss and employed by Heilmeyer [22] in his work on the optical absorption of plasma.

EXPERIMENTATION

Optimal Concentration of Oxalate for Human Blood.—Venous blood was placed under oil in narrow tubes containing sufficient heparin to prevent clogging. The blood was stirred well under oil with a glass rod. A series of narrow tubes was prepared, each containing 1 cc. of oil and 2 cc. of potassium oxalate solution, varying in concentration, at intervals of 0.1 per cent, from 0.1 to 2.0 per cent. One drop of the blood was delivered from a narrow, well oiled pipet under the oil in each tube; the tubes were shaken without disturbing the layer of oil, and the extent of hemolysis and crenation was read after five hours and again after twenty-four hours. Doubt as to hemolysis in the samples was eliminated by comparison of color against the 2 per cent tube; if the latter showed even slight hemolysis, the series was rejected.

In none of the fourteen experiments that were carried out was hemolysis observed with solutions containing 1.0 per cent or more of potassium oxalate. With the 0.9 per cent solution, three samples showed definite hemolysis, four showed none, and in seven the results were doubtful. With 0.8 per cent potassium oxalate, hemolysis occurred in every instance.

Crenation was observed microscopically by means of the sealed hanging drop. It occurred in every case with solutions containing 1.1 per cent or more of potassium oxalate; with the 1.0 per cent solution it was definitely noted in seven samples and absent in four, while in three instances the results were doubtful. With a 0.9 per cent oxalate solution, crenation was definitely absent in thirteen samples and questionable in one.

The optimal concentration lies between those at which crenation ceases and hemolysis begins, as in fragility tests (Gulland and

22. Heilmeyer, L., in Abderhalden: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1929, vol. 2, part 9, no. 9, p. 2263.

Gardall [23]); since hemolysis is the greater hazard in the estimation of dye, the 1.0 per cent solution was adopted, 2 cc. of which proved to contain sufficient anticoagulant for 10 cc. of blood.

Determination of Plasma Dilution.—For greater precision, the amount of blood taken was determined by weighing; the cell volume of the diluted sample was estimated (as soon as possible after collection) in the capillary hematocrit tube. For example:

Weight of tube with stopper, 2 cc. of oxalate solution, and oil..... 45.00 Gm.
Weight of tube with stopper, 2 cc. of oxalate solution, oil and blood... 52.00 Gm.

Weight of blood ..... 7.00 Gm.

Volume of blood [24]..... 7.00/1.06 = 6.6 cc.

The 6.6 cc. of blood was diluted to 8.6 cc.

The hematocrit value of diluted sample = 34 per cent.

The hematocrit value of undiluted blood. $\frac{34 \times 8.6}{6.6} = 44.3$ per cent.

The centrifuge tube containing the blood was well stirred before the blood was drawn into the hematocrit tube, and as the latter usually contained a little oil, the interface of plasma and oil was read as the divisor meniscus.

The corrected hematocrit value of the blood was used in calculating the dilution factor of the plasma, which varies with the volume of the sample and the individual hematocrit value, since it is only the plasma that is diluted.

Taking the foregoing example again, namely, 6.6 cc. of blood, of which 44.3 per cent is cell volume:

$$\text{Plasma volume} = 6.6\ (100\% - 44.3\%) = 3.7 \text{ cc. plasma.}$$

As the 3.7 cc. of plasma was diluted to 5.7 cc., i. e., to 1.54 of the original volume, the observed dye content of this particular plasma must be multiplied by 1.54.

Errors in the hematocrit value may be caused by failure to stir the blood before sampling, by loss of carbon dioxide, by incorrect concentration of oxalate and by prolonged stasis during bleeding. Loss of carbon dioxide may be prevented by a sufficiently thick layer of oil in the hematocrit tube.

It is probable that a prolonged or heavy stasis would result in a plasma too concentrated in dye, and plasma proteins. In order to reduce this danger to a minimum, we adopted a compression as nearly as possible equal to the diastolic blood pressure of the subject, for a period not exceeding fifteen seconds in all.

Spectrophotometric Examination of Dye Solutions.—A Koenig-Martens spectrophotometer (Martens and Greenbaum [25]) was employed over the range 420-667 millimicrons. The liquids were examined in Schulz cells containing water in the solvent chamber, the depth of cell being selected to yield a rotation of about 74

23. Gulland, G. L., and Gardall, Alexander: The Blood, New York, W. Green & Son, Ltd., 1925.

24. An average value, taken from various sources, of 1.06 was employed for the density of the blood. Deviations from this value are within the experimental error of the method in normal cases, but with patients suffering from some abnormality the actual density must be determined. The volume so estimated must, of course, check with the (less accurate) value obtained by direct reading in the centrifuge tube.

25. Martens, L., and Greenbaum, K.: Ann. de phys. **12**:984, 1903.

degrees on the scale of the analyzer (Adams and Rosenstein [26]). The ocular and objective slits were adjusted to the narrowest widths consistent with adequate visibility (Gibson et al.[27]). Five readings were taken with the absorbing medium in the path of each beam, matches being made on each side of the zero point by reversing the Schulz cell. This procedure eliminated the determination of the zero point, which was found to vary considerably with wavelength in our instrument (Gibson et al.[27]). The log. tangent of the average match angle in the first quadrant is added to the log. cotangent of the average match angle in the fourth quadrant to find the optical density of the sample at any given wavelength.

An example of the use of the procedure described in the body of this paper is afforded by the protocol of the case illustrated in chart 5. This is reproduced in table 2. An accurately measured volume (14 cc.) of a 1 per cent solution of the dye was injected into one arm of a normal man (weight, 64 Kg.), and blood

TABLE 2.—*Protocol of Case Shown in Chart 5*

Number	1	2	3	4	5	6	7	8	9
Time	30 min.	2 min. 48 sec.	4 min. 48 sec.	8 min. 3 sec.	10 min. 29 sec.	14 min. 34 sec.	22 min. 54 sec.	25 min. 23 sec.	36 min. 57 sec.
Dilution factor (C_2)	1.38	1.43	1.35	1.34	1.36	1.37	1.73	1.37	1.37
A	0.923	1.116	1.030	0.982	1.040	1.019	0.882	0.909	1.043
$A - \frac{C_1R_1}{C_2}$	0.640	0.843	0.741	0.691	0.753	0.734	0.656	0.625	0.759
B	0.783	0.967	0.880	0.791	0.934	0.879	0.859	0.698	0.969
$B - \frac{C_1R_2}{C_2}$	0.559	0.751	0.650	0.560	0.706	0.653	0.680	0.472	0.743
100 N	44.3	56.1	51.0	50.6	48.9	49.9	38.2	48.0	47.2
$\frac{100 \times C_2}{166.6} \cdot 10^{-4}$	36.8	48.3	41.3	40.7	39.9	41.2	39.7	40.2	38.9
$\frac{\left(B - \frac{C_1R_2}{C_2}\right)C_2}{166.6\ D} \cdot 10^{-4}$	43	69	56	48	61	57	75	41	61

Preliminary sample:
Dilution factor (C_1) = 1.38
R_1 = 0.283
R_2 = 0.225

Standard dye:
Dilution factor = 166.6
D_1 = 1.280 (net)
D_2 = 0.940 (net)

samples were withdrawn at timed intervals from the opposite arm, the technic that will be described in our second paper being exactly followed throughout. The samples, varying in volume from about 6 to 12 cc., were placed in weighed centrifuge tubes containing 2 cc. of 1 per cent potassium oxalate solution and from 1 to 2 cc. of oil; their weight was determined to within 0.01 Gm. After the dilution was mixed well, the hematocrit value was estimated on the sample so diluted. The dilution factor was computed from these values, by the method already described. The diluted blood was then centrifugated at 3,500 revolutions per minute for thirty minutes; the cell volume was read, and the sample was again

26. Adams, E. Q., and Rosenstein, Ludwig: J. Am. Chem. Soc. **36**:1452, 1914.
27. Gibson, K. S.; McNicholas, H. J.; Tyndall, E. P. T.; Frehofer, M. K., and Mathewson, W. E.: Scientific Papers of the Bureau of Standards, Washington, D. C., no. 440, 1922.

centrifugated for five minutes. This process was continued until a constant value had been reached. The clear plasma [28] was transferred by means of a pipet to the Schulz cell for spectrophotometric examination.

The dye-free control, collected immediately before the injection of dye, was tested in exactly the same manner. For the preparation of the dye standard, a 3 cc. portion of the diluted dye-free plasma was mixed with 5 cc. of a 1:100 dilution (in 0.9 per cent sodium chloride) of the dye solution employed for the injection.

Spectrophotometric measurements were made, in the manner already indicated, on dye-free plasma, dye standard and the various dye-containing samples. In all cases the net dye densities, obtained by subtracting the component optical densities of the plasma at corresponding wavelengths from those of the samples under examination $\left(\text{i. e., } A - \frac{C_1R_1}{C_2}\right)$ were employed for the calculation.

In table 2, all the symbols used are those employed in the text; R_1, A and D_1 are the determined optical densities on a 5 mm. unit cell depth at wavelength 516 microns, while R_2, B, and D_2 are the corresponding densities determined on the same basis at wavelength 536.3 microns. The density at wavelength 536.3 millimicrons was used for computation of the uncorrected intensity value:

$$\frac{\left(B - \frac{C_1R_2}{C_2}\right) C_2}{166.6\ D_2} \cdot 10^{-4}$$

Colorimetric comparison was impossible on account of the qualitative difference in color.

SUMMARY

1. The optimal concentration of potassium oxalate for human blood has been found to be 1 per cent.

2. The optical absorption of solutions of brilliant vital red is greatly altered by the presence of dissolved colloids and electrolytes, being increased in intensity by the former and decreased by the latter. Shifts in the region of maximum absorption also occur.

3. A method is described for the evaluation of the dye content of solutions of brilliant vital red in the presence not only of the normal plasma colors but of oxyhemoglobin.

28. The diluted plasma from fasting subjects is invariably water-clear. In one series, reported in our second paper, which extended over a protracted time, it was observed that samples of plasma from blood collected shortly after meals were cloudy. This condition was corrected by shaking the plasma with about 2 cc. of ethylene chloride and centrifugating.

DETERMINATION OF PLASMA VOLUME

II. THE RATE OF DYE MIXING *

S. GRAFF, B.S.

D. A. D'ESOPO, M.D.

AND

A. J. B. TILLMAN, M.D.

NEW YORK

In the first paper [1] a method for the accurate evaluation of brilliant vital red in the plasma was described. If the measurement of the dye concentration is to serve as an index of the total plasma volume, the mixing of the injected dye with the plasma must be complete throughout the circulation before there is any appreciable loss of dye. Two problems, then, would naturally follow: (1) to determine the time required for complete mixing of dye and plasma and (2) to find the rate of loss from the blood stream. These problems can be studied by determining the dye concentration in a series of samples of plasma taken at frequent measured intervals after the injection of the dye. The present communication deals with this study.

Measured volumes of dye of known concentration were injected into the median basilic vein of one arm, and 10 cc. samples were periodically removed from the corresponding vein of the other arm. The dye concentration was then estimated according to the procedure described in the first paper. The results obtained with three normal men and two nonpregnant women are shown in chart 1. The percentage ratio of the dye concentration in the plasma to that in the solution injected is plotted against the time that elapsed after injection. Zero time was taken at the end of injection, and the blood samples were timed at the end of withdrawal. The time of injection of the dye averaged about twenty-five seconds and the time of sampling was usually less than ten seconds.

It will be noted that each of the curves shown in chart 1 shows three rather distinct phases, viz.: (*a*) an initial rapid rise to a maximum

* Submitted for publication, Feb. 20, 1931.

* This work was aided by grants from the Chemical Foundation.

* From the departments of Biological Chemistry and of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons.

* From a thesis submitted by S. Graff in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Columbia University.

1. Graff, Samuel; and Clarke, H. T.: Determination of Plasma Volume: I. The Dye Method, this issue, p. 808.

peak, (*b*) a rapid fall to a sharp point of inflection and (*c*) a straight line with a gradual downward slope. In every case the first two phases occupy six minutes or less, irrespective of the values of the maxima. As a matter of fact, the precise height of the latter cannot be regarded as significant, owing to the impracticability of obtaining samples at more frequent intervals. The time value assigned to each point is also

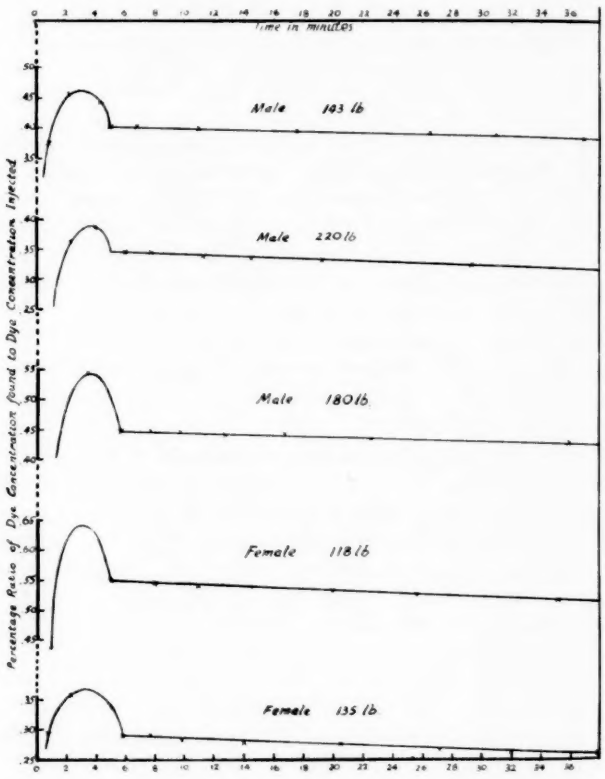

Time in minutes
Percentage Ratio of Dye Concentration found to Dye Concentration Injected
Male 193 lb
Male 220 lb
Male 180 lb
Female 118 lb
Female 135 lb

Chart 1.—Dye concentration in blood samples taken at intervals from normal men and normal nonpregnant women.

subject to doubt because of the time required to inject the dye and withdraw the samples, but this error cannot be more than thirty-five seconds. The important part of the curve is the straight line portion which uniformly begins between the fifth and sixth minute after injection of the dye and drops slowly enough to make the errors mentioned insignificant.

We make the following explanation of the curves. The initial rise is dependent on the rate of injection and on the actual time that is required for the dye to be carried from the median basilic vein of one arm to that of the other arm. As more and more dyed blood completes the circuit, the higher will be each successive reading until a peak is reached. At this point the dye concentration is maximal in the larger vessels in which the flow of blood is more rapid, but it is not yet equalized in respect to the entire circulatory system. The rapid fall noted in the curves is therefore not an actual loss of dye. Finally, a

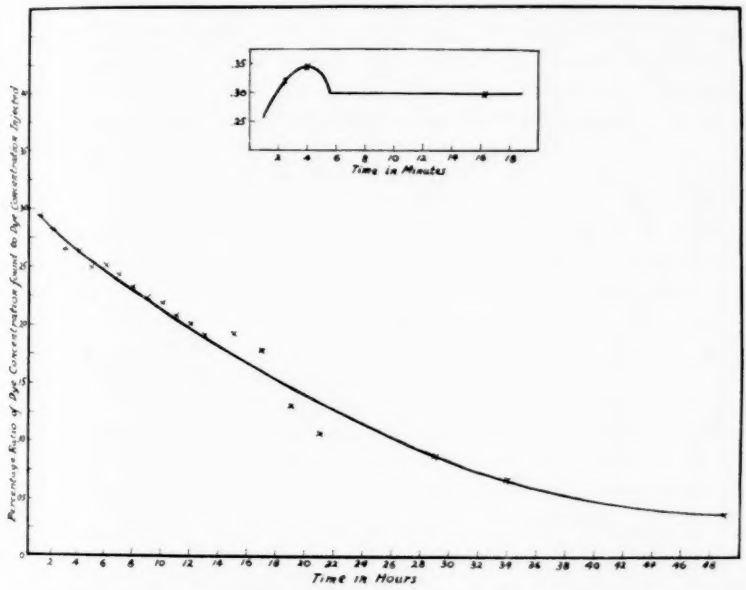


Chart 2.—Dye concentration in blood samples taken at intervals from a normal man.

point of equilibrium is reached when the dye is evenly distributed throughout the circulation; this corresponds to the point of inflection in the curves. To recapitulate: Over a period of from five to six minutes following the injection of dye, the concentration of the latter is in a constant state of fluctuation at any given point in the circulatory system until complete mixing has been attained, and this state of variable concentration is due, not to a rapid loss of dye, but rather to the differences in the rate of flow in the various parts of the circulatory system.

The slope of the straight line portion of the curve represents the actual loss of dye from the plasma. Unquestionably, some actual loss takes place during the first six minutes simultaneously with the changes in concentration, but this indeterminable loss is presumably small if it bears any relation to the rate of loss noted after the point of equilibrium is reached. If it were assumed that the drop in concentration as shown by the entire curve represents an actual rapid loss of dye, we should be obliged to draw the absurd conclusion that the rate of loss from the third to the sixth minute after injection is 120 times more rapid than from the sixth to the ninth minute, or, to put it in another way, that as much dye is lost during the second three minute period as in the subsequent six hours.

The experiment depicted in chart 2 gives additional support to the view that the drop from the peak is not due to excretion of dye. In this experiment the dye concentration was measured at intervals over a period of forty-nine hours after injection. The rate of loss is approximately 2.8 per cent per hour, with one-half the dye excreted at the end of twenty-two hours. The rate of loss of dye, as was recently demonstrated by H. P. Smith,[2] appears to be proportional to the dye concentration. According to Smith,[3] the loss to the intercellular spaces and the slow staining of cells comprise the chief mechanisms of excretion. Such an orderly process could not account for the rapid drop during the period from the third to the sixth minute. After this phase, the curve in chart 2 shows such a slow drop in dye concentration that no appreciable deviation in readings results even if the samples are obtained a few minutes after the equilibrium time is reached.

The presence of the peak has been observed by other investigators. Lamson and Rosenthal,[4] working with dogs, recorded irregularities involving a maximum after three minutes, in view of which they condemned the dye method as unreliable. Harris,[5] also using dogs, noted peaks, but interpreted the subsequent drop as indicating a rapid loss of dye from the general circulation. Erlanger [6] constructed curves from published data, which showed considerable variations during the first ten minutes. On the other hand, Rowntree [7] in a study of forty-seven cases observed no differences between the values at three and at six minutes, and these agreed within 2 per cent with those at two minutes.

2. Smith, H. P.: Bull. Johns Hopkins Hosp. **36**:325, 1925.
3. Smith, H. P.: J. Exper. Med. **51**:369, 1930.
4. Lamson, P. D., and Rosenthal, S. M.: Am. J. Physiol. **63**:358, 1923.
5. Harris, D. T.: Brit. J. Exper. Path. **1**:142, 1920.
6. Erlanger, Joseph: Physiol. Rev. **1**:177, 1921.
7. Rowntree, L. G.; Brown, G. E., and Roth, G. M.: The Volume of the Blood and Plasma in Health and Disease, Mayo Clinic Monograph, Philadelphia, W. B. Saunders Company, 1929.

The curves that we have described are sufficiently regular, we believe, to justify the conclusion that in normal individuals dye concentration in the circulating plasma reaches an equilibrium six minutes after injection of the dye, and that the value obtained at this time may be used for the calculation of the plasma volume. This, however, involves the assumption that the rate of loss of dye from the circulation as a whole is not higher during the first six minutes than it appears to be after that time. Extrapolation of the straight line part of the curve to zero time is of no value, since the loss of dye calculated in this way is within the probable error of the method.

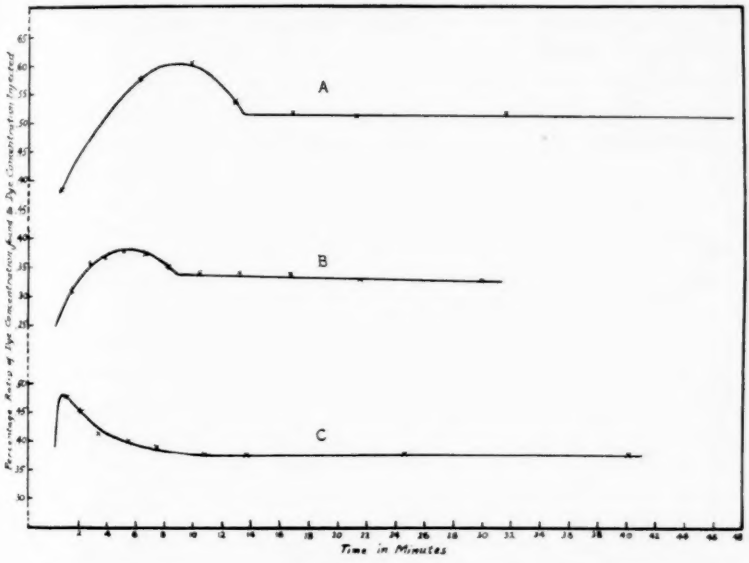


Chart 3.—Dye concentration in blood samples taken at intervals: *A*, from a patient suffering from arteriovenous aneurysm; *B*, from a normal pregnant woman in the seventh month of gestation, and *C*, from a normal woman in active labor.

It was of interest to us, in view of some proposed studies concerning the total blood volume in pregnancy, to attempt the same sort of experiment in patients whose circulatory systems were anatomically altered from the normal. Chart 3*A* shows the curve obtained in a case of a traumatic arteriovenous aneurysm of the subclavian artery. The patient, a man, aged 40, presented all the evidence of circulatory stasis in his right arm. The arm was markedly edematous; there were numerous varicosities, and the flow of blood through the veins was under arterial tension. Dye was injected into one of the veins of the

affected arm. Approximately twice as much time was required for the dye to reach an equilibrium in this case as was noted under normal conditions.

Observations were made in two cases of pregnancy. In the first one (chart 3*B*), that of a normal pregnant woman in the seventh month of gestation, the equilibrium time was reached at the end of about nine minutes, the shape of the curve showing that the delay was due chiefly to a slow rate of fall from the peak level. The second subject (chart 3*C*), a woman in active labor, received the dye thirty-seven minutes before delivery. Here again it is noted that complete mixing of dye and plasma requires between nine and ten minutes, although the peak is reached in a very short time. This delay in cases of pregnancy is in all probability due to the large uterine circulation.

The plasma from a sample of fetal blood, taken from the cord immediately after delivery, was a deep red, but when corrected for hemoglobin by the process described in our first paper it showed absence of dye.

EXPERIMENTATION

Preparation of the Dye for Injection.—A 1 per cent solution of brilliant vital red in 0.9 per cent sodium chloride was filtered three times through quantitative paper; 25 cc. portions were placed in wide-mouthed bottles, which were stoppered with cotton plugs wrapped in gauze. This precaution was taken to prevent lint from coming in contact with the solution.[8] The bottles were sterilized in the autoclave at 15 pounds' pressure for one-half hour. A graduated Record-type syringe with stopcock adapter, working smoothly without a lubricant, was calibrated for delivery. The volume of dye injected was computed on the basis of 1 cc. for 5 Kg. of body weight. The syringe was filled beyond that volume; air bubbles and excess dye were expelled through the adapter, and the stopcock was closed when the meniscus was opposite the calibrated graduation mark nearest to the computed volume. The dye remaining in the bottle was used for the standard as discussed in the preceding paper.

Preparation and Use of the Sample Tubes.—Graduated 15 cc. centrifuge tubes were used, each tube containing exactly 2 cc. of 1.1 per cent potassium oxalate solution and about 2 cc. of dry mineral oil. These tubes were stoppered and weighed with the contents to the nearest decigram.

Samples of blood were received by replacing the intravenous needles and introducing the blood under the surface of the oil. The delivery needles were oiled and drained before use. The tubes were stoppered and the contents were mixed by stirring with a glass rod. The volume of blood was determined by difference in weight as discussed in the first paper, the graduations in volume serving as checks.

The Experimental Routine.—The subjects rested, lying on the back, for thirty minutes preceding, as well as during the course of, the sampling. Procaine hydrochloride was injected near the site of the proposed puncture. A preliminary

8. We suggest the use of rubber-capped serum bottles, since evaporation deposits crystals that are not immediately soluble, rendering the solution unfit for intravenous use.

sample was taken from the median basilic vein, the needle left in situ, the injecting syringe attached, and the dye injected over a period of from twenty to thirty seconds. Zero time was taken at the end of the injection, and the other arm was prepared for sampling. A constant measured stasis was used for each venous puncture, the Baumanometer being used and compression adjusted so as to equal approximately the measured diastolic pressure. This pressure was held for fifteen seconds during the puncture and withdrawal of blood. When withdrawal was difficult or the blood clotted, the sample was rejected, since blood clots hold as high as 10 per cent of the dye (Rowntree, Brown and Roth [7]).

SUMMARY

1. When brilliant vital red is injected into the venous circulation, its concentration first reaches a maximum and then falls to an equilibrium value. In normal cases this value is attained within six minutes.

2. An explanation for this behavior is suggested, involving the assumption of rapid circulation through one part of the system and a more sluggish flow through another. This explanation is supported by the observations of delay in attainment of equilibrium in cases of pregnancy and of arteriovenous aneurysm.

3. The general loss of dye from the circulation amounts to from 10 to 20 per cent per hour.

4. In the routine determination of plasma volume the sample of blood should be withdrawn after not less than six minutes in normal nonpregnant subjects; in other cases, the mixing time should be determined by the withdrawal of several samples at intervals during the first twenty minutes.

5. A suggested routine technic for the determination of plasma volume is outlined.

BLOOD AMYLASE IN RELATION TO DISEASE OF THE PANCREAS*

FURTHER OBSERVATIONS

ROBERT ELMAN, M.D.
ST. LOUIS

Since the last publication [1] on blood amylase from this laboratory, an additional number of cases have been studied, which, with one or two exceptions, have confirmed the observations already made, i. e., that blood from patients with a normal pancreas has a normal blood amylase, whereas deviations from this normal are found only in cases of proved disease of the gland. Additional observations have also been made simplifying somewhat the technic of the test.

Using the viscosimetric technic as described in our original paper,[1] Wakefield, McCaughan and McVicar [2] recently reported observations in a series of twenty cases of tumors of the pancreas in which five showed increased values of blood amylase (12.3, 15.1, 38, 53 and 75 units). In the case with a value of 53, a pancreatic cyst was found; on the other hand, in a case with fat necrosis, 15.1 units were found. In two of the thirty cases in which the pancreas was normal, increased values of 15.7 and 24 were reported.

In the present and last series of our cases no values as high as 38 or 75 units were observed except in cases of acute pancreatitis and pancreatic cyst. It may be noted that early in our studies occasional high values were observed in normal plasma, but it was soon suspected that contamination with particles of saliva in the pipet had occurred. After scrupulously plugging all pipets and viscosimeters with cotton, no further instance of this kind was encountered. Attention was called in our last paper to the necessity for this precaution. So strong is the amylolytic power of saliva that a tiny particle of it may cause a marked drop in the viscosity of the starch solution.

The significance of very low values of blood amylase was discussed in our previous paper; that they indicate atrophy of the pancreas is

* Submitted for publication, Feb. 25, 1931.

* From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

1. Elman, R.; Arneson, N., and Graham, E. A.: Value of Blood Amylase Estimations in Diagnosis of Pancreatic Disease, Arch. Surg. **19**:943 (Dec.) 1929.

2. Wakefield, E. G.; McCaughan, J. M., and McVicar, C. S.: Amylase in Blood in Subacute and in Chronic Pancreatic Diseases, Arch. Int. Med. **45**:473 (March) 1930.

only partly confirmed by the cases herein reported. Seven observations of low blood amylase were made, but unfortunately in four of the cases no anatomic studies were possible. Of the other three cases, two came to autopsy: one showed definite atrophic changes of the acini (case 3: blood amylase, 3.5 units); the other (case 4) was that of a patient with a low oxygen-carrying capacity and heart failure, whose pancreas appeared normal anatomically, but whose blood amylase was low (1.5 units). Whether the circulatory failure affected the pancreatic acini and diminished their activity cannot be said. The microscopic picture, aside from evidence of chronic passive congestion, could not be expected to give such information. In the third case (case 1) the patient was operated on; biopsy of the pancreas, it is true, showed only scar tissue, which might be interpreted as evidence of atrophy, except that the specimen was very small and conceivably might have included only part of the capsule of the gland. The frequency of low values as reported by Wakefield, McCaughan and McVicar [2] both in the normal series as well as in those with tumors of the pancreas is in distinct contrast to our findings both in our last series and in the present series of cases.

Further comment on the present findings is hardly necessary, for the tables and protocols are self explanatory. It will be noted that in five cases normal blood amylase values were observed, and were confirmed by the finding of a normal gland in four cases, two at operation and two at autopsy. In the fifth case (case 2), though the tumor involved the pancreas, it was impossible to be sure from the extent of the growth and from microscopic study of the biopsy specimen whether the tumor originated in the pancreatic, cystic or common bile duct. It seemed apparent, however, from its location that it could easily have missed obstructing the pancreatic duct, and, after all, it is not the tumor itself but its secondary effect on the pancreatic ducts or acini that can be expected to produce changes in the blood amylase. This may, perhaps, explain the finding of normal values by Wakefield, McCaughan and McVicar [2] in some of their cases of tumor of the pancreas. The true relation can be established frequently only at autopsy.

Critical analysis of the present observations as to the practical value of the study of blood amylase in the diagnosis of pancreatic disease indicates its usefulness in several aspects. In case 11 the high amylase value added significant weight to the indications for operation, which the finding of an acute pancreatitis justified. In case 13 the value of the blood amylase was not utilized as an indication for operation, which if performed might have saved the patient's life. In case 14, one of a pancreatic cyst, the marked increase in blood amylase proved an important aid in the diagnosis and in the indications for operation. In a recently observed case the symptoms of acute disease of the upper

portion of the abdomen were so marked that pancreatic necrosis was suspected and operation was planned; the blood amylase, however, was normal. Operation was not performed, and the subsequent development with recovery of the patient pointed rather to coronary disease as the probable cause of the symptoms. In the chronic cases, in general,

TABLE 1.—*Cases in Which the Pancreas Was Examined at Operation or at Autopsy*

Case	Age	Sex	Clinical Diagnosis	Jaundice	Blood Amylase, Units	Anatomic Diagnosis and Comments
1	50	M	Carcinoma of stomach.....	0	1.1	Carcinoma of pancreas; operation, biopsy, atrophy of pancreas (?)
2	62	M	Carcinoma of pancreas.....	+	5.0	Carcinoma of pancreas or bile ducts; operation, biopsy
3	52	M	Carcinoma of pancreas.....	+	3.5	Carcinoma of pancreas with beginning atrophy; autopsy
4	37	M	Pulmonary emphysema.....	0	1.2	Normal pancreas; autopsy
5	56	F	Chronic cholecystitis.....	0	5.5	Normal pancreas; operation
6	55	M	Carcinoma of pancreas.....	+	5.1	Primary carcinoma of liver; normal pancreas; autopsy
7	53	F	Acute appendicitis.....	0	13.5	Acute pancreatitis; operation
8	50	M	Tumor of pancreas.....	0	6.0	Carcinoma of stomach; normal pancreas; operation
9	50	M	Carcinoma of pancreas.....	+	5.5	Carcinoma of bile ducts metastatic from cecum; normal pancreas; autopsy
10	32	F	Chronic cholecystitis.....	0	5.0	Normal pancreas; operation
11	18	F	Gallstone colic.....	0	35.0	Acute pancreatitis; operation
12	45	M	Stone in common duct.....	0	15.0	Tumor at head of pancreas; operation
13	54	F	Acute yellow atrophy of liver	+	150.0	Acute pancreatitis; stone in common duct; autopsy
14	46	M	Carcinoma of stomach.....	0	30.0	Pancreatic cyst; operation

TABLE 2.—*Cases with Abnormal Values for Blood Amylase in Which the Pancreas Was Not Examined*

Case	Age	Sex	Clinical Diagnosis	Jaundice	Blood Amylase, Units	Clinical Suggestions of Pancreatic Involvement
15	27	M	Stone in common duct.....	+	1.2	"Pancreatic asthenia"
16	49	F	Carcinoma of pancreas.....	+	10.0	Enlargement of gallbladder; epigastric pain radiating to left; extra-alimentary tumor; glycosuria
17	64	F	Diabetes.....	0	1.5	Cirrhosis of liver and palpable spleen, glycosuria
18	67	F	Carcinoma of pancreas.....	+	1.2	Epigastric mass; diarrhea; painless jaundice
19	48	M	Carcinoma of pancreas.....	+	2.1	Enlargement of gallbladder; painless jaundice
20	32	M	Acute abdominal condition(?)	0	55.5	Epigastric pain and tenderness; mild shock; patient refused operation

the deviations from the normal blood amylase have been less striking, and the usefulness of this indication has been less marked. In patients with painless jaundice the blood amylase may prove to be of importance in judging the probable value of a laparotomy. When carcinoma of the pancreas is present, a cholecystogastrostomy can frequently be done with at least temporary amelioration of symptoms. In those few cases in which the tumor is really not carcinoma but is due to inflammatory

enlargement, the operation may result in a cure. When the tumor has not involved the common bile duct and there is no jaundice (case 1), the blood amylase may be the only objective evidence of disease of the pancreas.

We have noted recently that the starch solution[3] prepared as described can be kept indefinitely at room temperature without losing its original properties, provided it is kept sterile and the portion to be used is boiled again. A batch of 100 cc. or more is made up in a cotton-stoppered flask. Whenever determinations are to be made, as large a portion as is needed is poured off into a separate receptacle (maintaining aseptic precautions by flaming the neck of the flask carefully), brought to a boil, filtered and transferred to the viscosimeters. This obviates the necessity of preparing a new starch solution each time and makes it possible to get a reading at any time within a half hour of drawing the blood.

SUMMARY

Twenty cases are reported in which the blood amylase was studied. In fourteen, anatomic observations of the pancreas were made, in nine cases by operation (including a biopsy in two), and in five by autopsy. With one exception, the findings have confirmed our previous observations; i. e., a normal blood amylase was found when the acini of the gland were normal; deviations from this normal value, either increase or decrease, were noted when the acini or ducts were diseased. The clinical usefulness of the test is discussed.

PROTOCOLS OF CASES

Case 1.—R. F., a man, aged 59, a cook, was admitted to Barnes Hospital on March 11, 1930, and was discharged on May 10. The onset of the illness was one month previous to admission, with pain in the epigastrium and back, especially at night and after meals, belching, anorexia, a loss of 20 pounds (9 Kg.) in weight and several attacks of severe vomiting. Constipation had been present for the year previous to admission and had become more severe. Examination gave negative results except for a poorly outlined questionable mass and tenderness in the midepigastrium. The test meal showed free hydrochloric acid. The x-ray series gave indeterminate results, a cholecystogram showed nonvisualization, and the liver function test[4] revealed 12 per cent retention in one-half hour (normal). The clinical diagnosis was carcinoma of the stomach. Operation was performed on April 20, 1930. The gallbladder contained stones. There were two large

3. The starch we have been using is that prepared by Merck and Company "according to the method of Lintner." A batch of it has been specially set aside by Merck and Company and can be obtained from them at Rahway, N. J., by specifying in addition, "for use in the determination of blood amylase."

4. The liver function test referred to is that of Graham and Cole. (Graham, E. A.; Copher, G. H.; Cole, W. H., and Moore, S.: Diseases of the Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1928).

nodules in the liver. Biopsy of one of these nodules showed carcinoma, probably arising from the acini of the pancreas. The pancreas was hard and also contained a mass. Biopsy showed fibrous but no acinar tissue. The blood amylase was determined one week after operation and showed 1.1 units.

Case 2.—B. V. J., a salesman, aged 62, was admitted to Barnes Hospital. The onset of the illness occurred two weeks before admission, with a mass, soreness and uneasiness in the right upper part of the abdomen; five days later there was jaundice, which became more severe. Every few years for the decade preceding admission, the patient had had numerous mild attacks suggestive of gallbladder pain which lasted a few days. Examination revealed intense jaundice, a palpable liver edge and a smooth epigastric tumor, probably of the gallbladder. The liver function test showed 30 per cent in one hour (marked retention) at one examination and 7 per cent in forty minutes (normal) ten days later. The blood amylase was 5.0 units (normal). A cholecystogram showed a persistent questionable mottled shadow. The jaundice increased under conservative treatment, and operation was performed on April 10, 1930. A large distended gallbladder containing stones, turbid fluid and cholesterol crystals was found. The proximal part of the gallbladder was densely adherent to the pancreas. On separation, a hard tumor was found involving the upper part of the head of the pancreas, the common duct and probably the cystic duct. Biopsy showed adenocarcinoma arising from either the pancreatic or the bile ducts.

Case 3.—W. W. W., a man, aged 52, a laborer, was admitted to Barnes Hospital on Sept. 16, 1929, and died on October 16. The illness was of nine months' duration, with gas and belching and a loss of 40 pounds (18.1 Kg.) in weight, but with no pain. Jaundice was present for four months. Edema and ascites developed toward the end of the illness. The blood amylase was 3.5 units (two examinations). Operation revealed a mass in the pancreas and a small shrunken gallbladder. At autopsy the mass was found to be a carcinoma obstructing the pancreatic duct, with definite though partial atrophy of the acini.

Case 4.—A. S., a man, aged 37, a laborer, was admitted to Barnes Hospital on March 9, 1930, and died on April 6. There had been symptoms of increasing dyspnea for the two years preceding admission, a cough for several years, and nausea and a suggestive epigastric lump for four or five months. In spite of some antisyphilitic treatment, the Wassermann reaction remained 4 plus. Constipation had been severe. Examination revealed dyspnea, cyanosis, pulmonary emphysema, vital capacity at 1,500 cc. and the oxygen capacity of the blood 19.7 per cent by volume. A gastric analysis revealed a marked hyperacidity. The blood amylase was 1.5 units. Digitalis and other treatment had no effect, and the patient died. Autopsy revealed extreme pulmonary emphysema and cardiac hypertrophy. The pancreas appeared normal grossly and on microscopic section and showed only vascular congestion and some swelling of the acini.

Case 5.—A. M. S., a housewife, aged 56, was operated on at Barnes Hospital on Dec. 3, 1929, for definite evidence of chronic cholecystitis, and a diseased gallbladder with stones was removed. The blood amylase before operation was 5.6 units. The pancreas was carefully examined at operation and was found to look and feel normal.

Case 6.—W. M., a plumber, aged 55, was admitted to Barnes Hospital on Sept. 29, 1929, and died on November 19. The onset of the disease occurred five years previous to admission, with bloating and epigastric pain radiating to the right side; relief was obtained with sodium bicarbonate. The pain became severe and constant and was uninfluenced by food two weeks before admission. Examination revealed

a large, firm liver. Slight icterus developed one week after admission, which increased. There was moderate ascites. The blood amylase was 5.1 units. The x-ray series showed evidence of an extra-alimentary tumor. Antisyphilitic treatment was given for three weeks without effect. Laparotomy and a biopsy of the liver were done. Autopsy one week later showed a characteristic case of primary carcinoma of the liver with a normal pancreas grossly and on microscopic examination.

CASE 7.—Q. P., a man, aged 53, was admitted to St. Mary's Infirmary on Oct. 9, 1929, for an emergent abdominal operation. Definite evidence of acute pancreatitis was found, including fat necrosis, reddish-brown fluid in the peritoneum and necrosis of the pancreas. The gallbladder and pancreas were drained, and the patient did fairly well. The blood amylase was determined two weeks after operation and was found to be 13.5 units.

CASE 8.—R. R. P., a man, aged 50, was admitted to the Frisco Hospital, complaining of epigastric discomfort, loss of weight, strength and appetite and pain in the lower part of the back and the abdomen for the past four months. There was vomiting on several occasions. A mass was felt in the epigastrium. The blood amylase on Oct. 29, 1929, was 6 units. Operation showed that the mass was due to a metastatic carcinoma of the omentum from a carcinoma of the stomach. The pancreas felt normal.

CASE 9.—E. H. R., a salesman, aged 54, was admitted to Barnes Hospital on May 28, 1929, and died on July 30. He had a definite alcoholic and syphilitic history. Four weeks before admission jaundice developed and increased gradually, but without any further symptoms other than a loss of weight of 25 pounds (11.3 Kg.), some anorexia and mild diarrhea. Examination showed deep jaundice and a large liver. The x-ray series gave indeterminate results. The blood amylase was 5.5 units. Operation, on June 1, 1929, revealed a collapsed gallbladder, a shrunken and sclerotic liver and numerous malignant nodules along the common duct and behind the peritoneum. The pancreas was normal to palpation. At autopsy a colloid carcinoma of the cecum was found with metastases to the liver and mesenteric nodes. The pancreas was normal grossly and on section, and in spite of much postmortem autolysis, showed intact acini that presented no pathologic change.

CASE 10.—E. S., a housewife, aged 32, was admitted to the City Hospital on June 1, 1929, with a diagnosis of chronic cholecystitis. The blood amylase was 5 units. The gallbladder was removed at operation, at which time the pancreas was seen and felt and judged to be normal.

CASE 11.—E. E., a housewife, aged 18, was admitted to the City Hospital on Oct. 15, 1929, with a diagnosis of gallstone colic. For five days she had had repeated attacks of severe epigastric pain, nausea and vomiting. On examination there were found evidence of moderate prostration, slight cyanosis and tenderness and muscle rigidity over the epigastrium. The blood amylase was 35 units. Operation revealed extensive fat necrosis, bloody peritoneal fluid and acute pancreatitis. The patient had an uneventful recovery following drainage of the pancreas and gallbladder.

CASE 12.—P. N., a laborer, aged 48, was operated on at the City Hospital, on Aug. 10, 1929, for cholecystitis, at which time the gallbladder and appendix were removed. At that time the pancreas felt normal. A persistent biliary fistula resulted, which lasted for five months. The blood amylase at this time showed 15 units. At operation a tumor at the head of the pancreas was found. A biopsy was

not deemed safe, but the fistula was implanted into the duodenum with the aid of a rubber tube; recovery was uneventful.

CASE 13.—V. G., a housewife, aged 54, was admitted to the City Hospital on June 29, 1930, profoundly sick. A history was not obtainable. Examination revealed moderately severe jaundice, a temperature of 99 F., a pulse rate of 140, moderate prostration and tenderness over the epigastrium. The blood amylase was 150 units. In spite of conservative treatment, the patient became steadily worse and died thirty-six hours after admission. Autopsy showed a cirrhotic liver, and stones obstructing the common duct but none at the ampulla. The pancreas was red and swollen, and numerous areas of fat necrosis were present in the omentum and retroperitoneal fat.

CASE 14.—J. W., a man, aged 56, was seen in the outpatient department on May 28, 1930. He gave a history of increasing attacks of vomiting for one year accompanied by cramplike pains with no relation to meals; there had been constipation and a loss of 72 pounds (32.7 Kg.) in weight. On examination, there was a hard mass in the epigastrium. A diagnosis of carcinoma of the stomach was made, and the patient was admitted to Barnes Hospital. The blood amylase was 30 units. Gastric analysis showed a high fasting acidity of 95 degrees. According to the report on the x-ray series made after a barium sulphate meal, the tumor was extra-alimentary, retroperitoneal and probably a pancreatic cyst. Operation on June 18, 1930, revealed a cyst which was drained of a liter or more of straw-colored fluid. There were stones in the gallbladder. Analysis of this fluid showed that it contained 1,500 units of amylase. Tests for trypsinogen and lipase were not made. There was a necrotic mass in the bottom of the cyst which was removed. Recovery was uneventful.

CASE 15.—L. F., a laborer, aged 29, with a diagnosis of stone in the common duct with jaundice, was operated on at Barnes Hospital. The blood amylase was 1.2 units. At operation the gallbladder, containing numerous stones, was excised, and many stones were removed from the common duct, which was drained. The pancreas was not examined. The postoperative course, however, was marked by extreme asthenia, anorexia and vomiting, which seemed to be characteristic of the condition of pancreatic asthenia as described by Whipple.[5] The patient recovered after several weeks, and was discharged from the hospital well.

CASE 16.—M. H. R., a housewife, aged 49, was admitted to Barnes Hospital on Feb. 11, 1929, and died on March 7. The onset of the illness occurred six months before admission, with a mass in the right upper quadrant of the abdomen which caused discomfort. There was pain in the epigastrium extending across the upper portion of the abdomen, especially after eating meat. Four months later the pain became constant and sharper and radiated to the left side. There was a loss of 25 pounds (11.3 Kg.) in weight, with increasing weakness. Examination revealed a large liver and a rounded mass in the epigastrium, probably the gallbladder. The blood amylase was 10 units. Roentgen examination of the chest showed mottling suggestive of metastatic carcinoma. Roentgen examination with a barium sulphate meal showed "extragastric upper retroperitoneal tumor." There was transient glycosuria. The blood sugar was normal. The patient died. Autopsy was not performed.

CASE 17.—S. A. D., a housewife, aged 64, was admitted to Barnes Hospital. There was a definite diagnosis of diabetes. The liver and spleen were both palpable, making a clinical diagnosis of chronic pancreatitis likely. The blood amylase was 1.2 units.

5. Whipple, A. O.: Ann. Surg. **78**:1468, 1923.

CASE 18.—L. M., a housewife, aged 67, was admitted to Barnes Hospital on Nov. 25, 1929, and died on Dec. 29. The onset of the illness occurred four months previous to admission, when she had an attack of discomfort and fulness in the upper part of the abdomen lasting two hours, with no pain, nausea or vomiting. Three months later severe diarrhea developed, which was controlled by medicine, and, one week afterward, painless and progressive jaundice. The blood amylase was 1.2 units. A firm, irregular mass was felt in the epigastrium on examination. The x-ray series gave negative results. The liver function test showed 7 per cent (normal). The patient died suddenly. Autopsy was not performed.

CASE 19.—C. E. S., a farmer, aged 48, was admitted to Barnes Hospital on April 3, 1929, and died on April 8. There had been painless jaundice and weakness at the onset, a loss of weight of 25 pounds (11.3 Kg.) in one year, and abdominal swelling for several months with a recent increase. Examination revealed an enlarged liver and gallbladder and ascites of 3,500 cc. The blood amylase was 2.1 units. The patient died suddenly. Autopsy was not performed.

CASE 20.—O. W., a Negro woman, aged 35, was admitted to the City Hospital on Feb. 19, 1930, with symptoms of severe epigastric pain, vomiting and a thready pulse; white blood cells numbered 26,500. The temperature was 98 F. There was localized tenderness in the midepigastrium, with muscle rigidity. The blood amylase was 55.5 units. The patient refused to undergo operation; under conservative treatment she gradually became better, and was discharged on March 3, 1930.

I. GOLDSTEIN'S HEREDOFAMILIAL ANGIOMATOSIS WITH RECURRING FAMILIAL HEMORRHAGES (RENDU-OSLER-WEBER'S DISEASE) *

HYMAN I. GOLDSTEIN, M.D.
CAMDEN, N. J.

In the opening paragraph of his paper on "Gastric Hemorrhage Due to Familial Telangiectasis," Boston [1] stated:

> A cursory survey of the literature disclosed records of 3 cases of recurrent rectal hemorrhage, one of oral bleeding and one of hematemesis which had been accompanied by cutaneous telangiectases. Wilson gave us the first recorded instance of rectal bleeding from telangiectases in 1896; Fox recorded a case in 1908; Phillips in 1908 cites the case of an extensive telangiectasis of the skin and mucous surface of the mouth with hemorrhages from the pharynx, and possibly from the stomach. Hutchison and Oliver's patient experienced recurrent rectal hemorrhage; and Pringle in describing his case alludes to recurrent attacks of vomiting blood.

Boston stated further that telangiectasia has not been considered in connection with painless hemorrhage of either gastric or rectal origin, and that the familial etiologic nature of the disease is evidenced in the report of his cases and in all the records that he cited from the literature.

The late Dr. Boston overlooked a number of cases, including my own [2] and others that have been reported from January, 1921, to December, 1930, inclusive, chiefly the cases reported between 1876 and 1930.

REVIEW OF THE LITERATURE

The first case that I [3] reported showed oral bleeding; the patient bled from the tongue and the lips. (This patient just died [July, 1931] as

* Submitted for publication, Jan. 3, 1931.

* A second paper on this subject with clinical reports of my cases will be published later.

* This subject was discussed by me with lantern demonstration before the Prof. L. A. Nekám Dermatologic Clinic and the Prof. Baron A. Korányi Medical Clinic, Royal University, Budapest, Hungary; before the Hungarian Dermatological Society in October, 1931, at Budapest; before the American Medical Association of Vienna, in October, 1931, and before a group of visiting physicians and medical staff of the Prof. Paul Morawitz Medical Clinic, Leipzig University, Leipzig, Germany (1931).

1. Boston, L. N.: Gastric Hemorrhage Due to Familial Telangiectasis, Am. J. M. Sc. **180**:798 (Dec.) 1930.

2. Goldstein, H. I.: Hereditary Hemorrhagic Telangiectasia with Recurring (Familial) Hereditary Epistaxis, Arch. Int. Med. **27**:102 (Jan.) 1921; Familial Epistaxis, J. M. Soc. New Jersey **19**:50, 1922; M. Times, New York **58**:208 (July) 1930; Hereditary Epistaxis, Internat. Clin. **3**:148 (Sept.) 1930; **4**:253 (Dec.) 1930.

3. Goldstein (footnote 2, first reference).

the result of severe recurrent hemorrhages [nose] and grave anemia, at Atlantic City, N. J. In 1918, she had hemiplegia from telangiectatic bleeding [cerebral].) In Coe's [4] first case (1906) there was bleeding from the mouth; this was also reported at a later date by Osler.[5] The patient in Kelly's [6] second case (1906) bled from the tongue and the lips. Phillips' [7] patient (1908) bled from the tongue and the roof of the mouth. The patient's father bled from the tongue, and the patient's sister died of hemorrhage from the gums. The patient's child bled from "spots" on the tongue. In this family there were four cases of oral bleeding.

Ersner (1930) stated that the fathers of two of his three patients had gastric hemorrhages. These cases were cited as examples of familial telangiectasia.

Guthrie [8] (1902) reported that twelve members in one family suffered from hematuria, and that the third daughter of an affected mother had hematemesis and nosebleed but no hematuria.

Foggie's [9] patient (1928) had hematuria and nosebleed, and many of the members of the patient's family bled from the tongue, the nose and the fingers. Rendu's [10] patient (1896) bled from the mouth, and the patient's father was subject to melena.

In discussing Phillips' [7] case, Fox [11] (1908) mentioned a case of multiple telangiectasias with bleeding from the rectum; a sister of the patient had had a similar condition.

Thomson and Lamb's [12] patient (1928) had severe bleeding from the mouth. At times blood ran "in a stream from the mouth." Her father was similarly affected.

Josserand's [13] patient (1902), a woman, bled from the gums and the tongue. Harper's [14] patient (1929) bled from the gums and the

4. Coe, John M.: The Treatment of Purpuric Conditions and Hemophilia J. A. M. A. **47**:1090 (Oct. 6) 1906.

5. Osler, W.: Bull. Johns Hopkins Hosp. **18**:401, 1907.

6. Kelly, A. B.: Glasgow M. J. **65**:411 (June) 1906.

7. Phillips, S.: Proc. Roy. Soc. Med. **1**:64 (Jan. 10) 1908.

8. Guthrie: Lancet **1**:1243, 1902.

9. Foggie, W. E.: Hereditary Haemorrhagic Telangiectasia with Recurring Hematuria, Edinburgh M. J. **35**:281 (May) 1928.

10. Rendu: Gaz. d. hôp. **49**:1322, 1896.

11. Fox, T. C.: A Case of Bilateral Telangiectasis of the Trunk, Brit. J. Dermat. **20**:145, 1908.

12. Thomson, A. P., and Lamb, F. W. M.: Case of Hereditary Familial Telangiectasis, Birmingham M. Rev. **3**:259 (Sept.) 1928.

13. Josserand: Bull. Soc. méd. d. hôp. de Lyon **1**:244, 1902.

14. Harper, R. A. J.: Multiple Hereditary Telangiectasis with Recurring Haemorrhages, Newcastle M. J. **9**:182 (April) 1929.

tongue, and had black stools. Schwartz'[15] patient (1925), a woman, bled from the tongue.

Hutchison and Oliver[16] reported three cases. John G., aged 49, a carman, bled from the gums, the mouth and the rectum, and vomited blood that he had swallowed. The father of this patient, aged 77, bled from the gums, and occasionally from the rectum.

Sequeira's[17] patient (1913), a woman, aged 55, bled from the tongue. Pringle[18] reported that only one of the daughters of his patient had occasional epistaxis. The other five children were in good health.

Osler[19] (1901) mentioned Rendu's[10] patient, a man, aged 52, whose father had repeated attacks of melena. Wilson's[20] patient (1869), a man, aged 30, bled from the nose and the gums (angiomas), but this was not a familial condition. Emily B., a patient of Fox[11] (1908), had marked epistaxis in childhood, and recent rectal bleeding. Sigmoidoscopic examination showed normal mucous membrane. Fox himself questioned whether his case belonged to the familial type. The second case cited by Osler[19] (1901) was in a man, aged 55, who bled from the lips, the nose and "spots" on the face; he vomited material resembling coffee-grounds. In the stomach were a dozen round angiomas (telangiectasias) and a cancer. Osler[21] stated that in 1904 (family 10) he saw a patient, aged 53, who bled from the nose and from spots on the face, the head and the arms, and frequently from the mucous membrane of the mouth. He cited another instance (family 7 [1907]) in which one sister of the two brothers who were his patients bled from the nose, and one sister bled from both the nose and the mouth.

Barford's[22] patient (1926) had severe recurrent hematemesis, nosebleed and hematuria.

Weber studied this subject exhaustively from 1902 to 1930, and in one of his papers in 1924, he[23] discussed gastric and rectal bleeding in this disease.

A number of instances of hemoptysis (Libman and Ottenberg,[24] 1923; Arrak, 1923) and hematuria have been reported in this disease.

15. Schwartz, V. J.: Hereditary Hemorrhagic Telangiectasis, Minnesota Med. **8**:551 (Aug.) 1925.
16. Hutchison and Oliver: Quart. J. Med. **9**:67, 1916.
17. Sequeira, J. H.: Brit. J. Dermat. **25**:154 (April) 1913.
18. Pringle: Proc. Roy. Soc. Med. **6**:129, 1912.
19. Osler, W.: Bull. Johns Hopkins Hosp. **12**:333 (Nov.) 1901.
20. Wilson, E.: J. Cutan. Med. **3**:198, 1869.
21. Osler, W.: Quart. J. Med. **1**:55, 1907.
22. Barford, L. J.: A Case of Recurrent Melæna, Guy's Hosp. Rep. **76**:97, 1926.
23. Weber, F. P.: Brit. J. Child. Dis. **21**:198, 1924.
24. Libman, E., and Ottenberg, R.: Hereditary Hemoptysis, J. A. M. A. **81**:2030 (Dec. 15) 1923.

Fig. 1.—Telangiectasias on the face, tongue, finger and nasal septum. This case was first reported in the ARCHIVES OF INTERNAL MEDICINE (**27**:102 [Jan.] 1921). The patient died in Atlantic City in July, 1931, as the result of severe secondary anemia following often repeated severe hemorrhage from the nose. (Goldstein: Internat. Clin. **3**:148, 1930).

Guthrie,[8] Henle,[25] Atlee,[26] Hurst,[27] Aitken,[28] Foggie,[9] Barford,[22] Mayou,[29] Apert [30] and others reported instances of hematuria. Perhaps the cases of hematuria reported by Hicks of Boston and Peters of Portland, Me., were also due to telangiectasias.

Kofler's [31] patient (1908) bled from the lips and the nose. Langmead's [32] patient (1910) bled from the tongue, the nose and spots on the face. Gjessing's [33] patient (1916) also bled from the mouth and the nose. Pons, Meine and Blenkle's [34] cases of gastrostaxis and gastric bleeding (1929) may have been due to telangiectasias, as may also those reported by Sir William Hale White.[35] Waggett's [36] patient (1908), a man, aged 55, bled from the lips, the face and the nose. His sister had the same symptoms as he had. Fox [11] (1908) mentioned Anderson's [37] case of rectal bleeding (1898) and found difficulty in classifying this case; Fox did not believe that his own case belonged to the familial group.

Boston,[38] in his paper on "Inherited Epistaxis," mentioned Kelly's [6] case of bleeding from the tongue, Galloway's [39] patient (1908) who bled from the mouth and the pharynx, and Anderson's [37] patient who suffered from intermittent attacks of rectal hemorrhage. He also cited Ullmann's [40] case of bronchial and gastric hemorrhages (1896). At autopsy small angiomas were found in the skin, bronchi, nasal mucosa and rectum and on the surface of the liver and urethra. Boston stated: "Goldstein (1921) found thirty (30) *case reports,* making in all forty-one (41), furnished by the literature." Up to 1920, I found thirty-one *families,* in a study of the literature, and up to June, 1931, inclusive, there were about ninety or ninety-five families and about 500 or 550

25. Henle: Arch. f. Dermat. u. Syph. **143**:461, 1923.
26. Atlee: St. Barth. Hosp. J., December, 1901.
27. Hurst, A. F.: Guy's Hosp. Rep. **73**:368 (July) 1923.
28. Aitken: Lancet **2**:444, 1909.
29. Mayou: Proc. Roy. Soc. Med. (clin. sect.) **1**:66, 1907-1908.
30. Apert, quoted by Hurst (footnote 27).
31. Kofler, K.: A Case of Naevus Pringle of the Skin, Wien. klin. Wchnschr. **21**:570, 1908.
32. Langmead: Proc. Roy. Soc. Med. **3**:109, 1909.
33. Gjessing, E.: Dermat. Ztschr. **23**:193, 1916.
34. Pons, C. A.; Meine, B. M., and Blenkle, V. A.: Certain Relationships of Gastric Hemorrhage and Gastrostaxis, J. M. Soc. New Jersey **26**:143 (Feb.) 1929.
35. White, W. H.: Some Forms of Haemorrhage Which are Difficult of Explanation, Lancet **1**:416, 1912.
36. Waggett, E. B.: Proc. Roy. Soc. Med. **1**:70, 1908.
37. Anderson, W.: Brit. J. Dermat. **10**:114, 1898.
38. Boston, L. N.: Inherited Epistaxis, M. Times, New York **58**:68 (March) 1930.
39. Galloway, J.: Proc. Roy. Soc. Med. **2**:109, 1908.
40. Ullmann, C.: Arch. f. Dermat. u. Syph. **35**:100, 1896.

persons affected with this disease, on record in the literature of the world. Boston also mentioned instances of gastric hemorrhage and reported a case in a man, aged 56. Several members of the family suffered from epistaxis. The man complained of constipation, attacks of tenderness over the abdomen, followed by faintness,

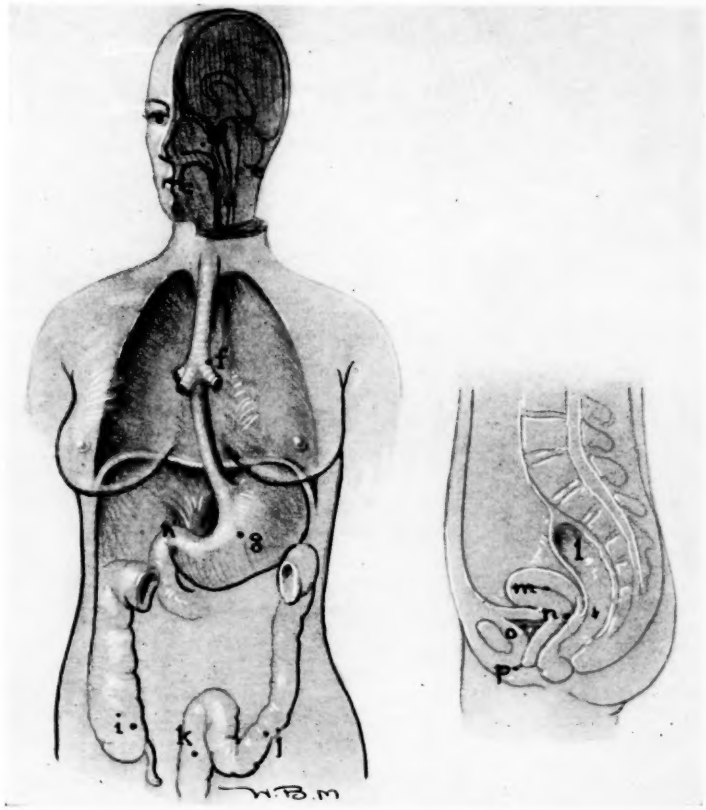


Fig. 2.—Points from which hemorrhage may occur in Goldstein's disease (hereditofamilial angiomatosis). (Goldstein: Internat. Clin. **3**:148, 1930.)

nausea and an unusual sense of fear. He suffered from nosebleed. Following each of the attacks of indefinite syncope, he experienced intense thirst and gastric distress, which he termed hunger pain. At various intervals, he vomited blood. Before consulting Boston, he had considerable soreness in the epigastrium, with slight tenderness over the pylorus and gallbladder and profuse bleeding from the nose. He

vomited blood-stained fluid during the first week that he was under Boston's care.

Fitz-Hugh, Jr.,[41] reported a case in a patient whose brother died of hemorrhages from the throat, which in all probability were from pharyngeal telangiectasias. He stated also that "several of the patients reported have had metrorrhagia and menorrhagia without any obvious cause, indicating the probability of telangiectases in the mucosa of the birth canal." His own patient, aged 37, had metrorrhagia and menorrhagia at intervals from puberty until her first pregnancy; she also bled from spots on her tongue, and had nosebleed.

Richardson's[42] patient (1917) had gastro-intestinal hemorrhages (melena) before epistaxis appeared.

Giffin's[43] third patient, a man, aged 36, bled from the nose. The spleen was barely palpable. There were buried and injected capillaries on the inferior turbinates. Petechiae (?) were present on the roof of the mouth and on the upper lip.

Arrak's[44] patient (1925), a woman, aged 53, bled from the nose, the finger and the tongue. Her father died from nosebleed. Arrak reported another case (1923) in a woman, aged 49, who had telangiectasias and nosebleed. One daughter had hemoptysis about once a month; she died of pulmonary hemorrhage. Physicians were unable to find any evidence of tuberculosis, clinically or roentgenographically.

Miller's[45] patient (1923) bled profusely from the nose, and occasionally from the right side of the lower lip from a "well marked dilated arteriole." Miller thought that the condition followed smallpox, three years previously.

Felix Semon (1907-1908) reported Phillips'[7] case in a woman, aged 56, who suffered from bleeding from the mouth and later from the nose. Her father suffered from violent epistaxis and bleeding from the tongue. Her sister died from hemorrhage of the gums.

Gjessing's[33] first patient (1916), a man, aged 52, bled from the nose and several times had hemorrhages from the angiomas of the face and the mouth at the same time. Most frequently he bled from the nose, much more rarely from the angiomas of the cheeks and of the tongue. He had had hemorrhages from the conjunctiva of the right eye three times, fifteen years previously. Gjessing's second patient, the son of the patient in case 1, aged 30, had profuse nosebleed, and once

41. Fitz-Hugh, T., Jr.: Am. J. M. Sc. **166**:884, 1923.

42. Richardson: Am. J. M. Sc. **154**:95, 1917.

43. Giffin, H. Z.: Familial Epistaxis Without Telangiectasia, Am. J. M. Sc. **174**:690, 1927.

44. Arrak, A.: Hereditary Hemorrhagic Telangiectasis, Deutsches Arch. f. klin. Med. **147**:287, 1925.

45. Miller, J. W.: Telangiectasis of Nose and Lips with Severe Epistaxis, Laryngoscope **33**:365, 1923.

had hemorrhage from the mouth. He had angiomas on the face, the tongue and the hard palate. The patient also had cardiac disease, hemorrhagic retinitis and severe secondary anemia. Gjessing reviewed the literature and the histories of eighteen families, which had been reported in the English, French and American literature.

One of Chiari's patients bled from the nose and from the gums. Chiari [46] (1887) reported cases of hereditary hemorrhagic telangiectasia in two families.

Chauffard's [47] patient (1896), a married woman, aged 50, bled from the nose, from the frontal region near the hair line and from the right eyebrow, left ear, tongue, palate, gums, fingers and toes.

Fig. 3.—*A*, telangiectasias on the face and lips. (Ullmann: Festschrift zu Ehren von M. Kaposi, 1900.) *B*, the first illustration on the subject in the literature. (Ullmann: Arch. f. Dermat. u. Syph., 1896, vol. 35.)

Hanes [48] (1909) reported cases in two families. In case 2, a fireman, aged 33, the son of his first patient (a woman, aged 53), had serious hemorrhages from telangiectasias of the lips and the tongue, and profuse hemorrhages from the third left finger-nail. He had telangiectasias on the cheeks, lips, tip of the tongue and gums; there were none on the nasal mucous membrane. There were many smaller telangiectasias on the tips of the fingers, and two under the third left

46. Chiari, O.: Erfahrungen auf dem Gebiete der Hals-und-Nasen-Krankheiten, Vienna, Toepflitz & Deuticke, 1887, p. 60.

47. Chauffard: Bull. et mém. Soc. méd. d. hôp. de Paris **13**:352, 1896.

48. Hanes, F. M.: Bull. Johns Hopkins Hosp. **20**:63, 1909.

finger-nail. In case 3, a man, aged 32, a son of the first patient, bled from telangiectasias of the face and the lips. He suffered during his whole life from nosebleed; there were no telangiectasias on the nasal mucous membrane, but the capillaries were dilated.

Laffont's [49] patient (1909) was a woman, aged 47. A brother often spit blood, presumably from the pharynx. The daughter of this patient, aged 25, had suffered from epistaxis since childhood and had also had hemorrhage from telangiectasias of the face and the gums.

De Santi (1908), in discussing Waggett's[36] case, said that he had examined a similar case in a woman who had nosebleed but no growth or venules (nevoid tissue). She had also extensive hemorrhages from the bowel, but sigmoidoscopic examination showed that the lower part of the bowel was normal.

Conner and Bumpus [49a] (1927) discussed essential hematuria and its relationship to purpura hemorrhagica. There was a history in five cases (of the twenty-two studied) of hemorrhage in other members of the family: epistaxis, intestinal hemorrhage, hematuria and hemoptysis. Some of these cases may have been examples of Osler's disease.

Harper's [14] patient (1929), a man, aged 45, bled from the nose, the gums and the tongue. He had a large number of telangiectasias on the cheeks, the tips of ears, the gums, the tongue and the palate. He also noticed black stools. Four of his daughters were affected, as were also his sister and his father. His eldest daughter, aged 18, suffered from epistaxis, and had excessive menstruation.

One of Steiner's [49b] patients, Mrs. A. T., aged 33, had had nosebleed since childhood; she bled also from the tongue, the pharynx and the hard palate. These hemorrhages became more profuse, especially during eating. Another of Steiner's patients, Mrs. D. E., aged 25, bled from the nose, sometimes five or six times a day. She bled also from the tongue. One of his patients, E. N., aged 41, bled from the nose and the gums. Steiner (1917) reported three families affected with this disease and reviewed the cases previously reported in a total of twenty-eight families.

There were four affected members in the family treated by Van Wagenen [50] (1912). One of the patients, aged 32, bled from the tongue and the nose. Telangiectasias were seen on the nasal mucous membrane and on the tongue, face and arms.

Verneuil [51] (1894) thoroughly discussed juvenile hereditary epistaxis, and expressed the belief that there is a close relationship between

49. Laffont: Presse méd. **17**:763, 1909.

49a. Conner, H. M., and Bumpus, H. C., Jr.: Am. J. M. Sc. **173**:176, 1927.

49b. Steiner, W. R.: Telangiectasia, Arch. Int. Med. **19**:194 (Feb.) 1917.

50. Van Wagenen, C. D.: Med. Rec. **109**:81, 1912.

51. Verneuil: Bull. Acad. de méd. **21**:548, 1894.

rheumatism and the familial incidence of epistaxis in childhood and in early youth. He quoted Martineau as saying that ancient authors reported that patients who have had nosebleed in their childhood are more apt to have rheumatism than others. He stated that a history of epistaxis was often found in adults who suffered from tuberculosis or rheumatism. Chomel in his essays on rheumatic fever and Hippocrates in the Prorrheticon have similarly commented on this relationship. Duroziez (1880) reported such cases.

Verneuil has often seen epistaxis in vigorous young persons, children of arthritic parents, who later became arthritic themselves; he has seen several children who had migraine. He expressed the belief that the subjects of juvenile epistaxis often bleed later on, not only from

Fig. 4.—Osler's case. (Osler: Quart. J. Med. **1**:55, 1907.)

the nose, but from the lungs, anus and uterus, without any organic change. Verneuil reported a family suffering from hereditary epistaxis. He disagreed with Forgues and Besnier, who claimed that this form of epistaxis in families is generally considered hemophilia. He did not believe that there was such a thing as idiopathic hemophilia. He maintained that the cause of the epistaxis in the family cited by him was "rheumatism and liver disease." He mentioned a male infant who bled from the nose and the anus.

Levine, Andren and Homans [52] (1930) also showed the close relationship of epistaxis and rheumatism in a study of a series of cases. I [53] also referred to this in my paper on "Hereditary Epistaxis."

52. Levine, S. A.; Andren, T., and Homans, K. A.: New England J. Med. **203**:832, 1930.

53. Goldstein (footnote 2, third reference).

Libert [54] reported a case in a man, aged 45, who had blood in his stools. No trace of ulcer was found at operation. The mucosa was congested, and the small veins increased in size. After the gastroenterostomy, the patient had no further symptoms.

One of van Gilse and Postma's [55] patients (1928), a woman, aged 23, had punctiform hemorrhages and angiomas on the left cheek, the back, the alae of the nose, the left forearm and the dorsum and palm of the hand. She had suffered from almost daily nosebleed since her sixth year. Van Gilse and Postma reported four cases of Osler's disease or Goldstein's heredofamilial angiomatosis occurring in two Dutch families.

About a year later van Gilse [56] and his co-workers stated that they had observed six families similar to the ones previously cited. In one of their cases, a single brother of their patient's father suffered from frequent hemorrhages from the tongue. The patient's second sister died at the age of 34. Her condition was first diagnosed as pernicious anemia (?). She bled from the nose and from the gums. Hers was a severe case of Osler's disease. A third sister of the patient died at the age of 18 from a severe blood condition; she suffered from epistaxis.

In 1911, Osler [57] reported two cases of Rendu-Osler-Weber's disease. The father and the daughter were affected. The daughter, aged 35 (seen by Dr. Anderson, of London), suffered from infancy from recurrent epistaxis and hemorrhages from the lips and the tongue. She had telangiectasias on the nose, cheeks, lips, tongue and fingers.

Curschmann's [58] first patient (1930), a man, aged 54, had telangiectasias on the cheeks, the lower lip and the soft palate. He suffered from epistaxis every two weeks, frequently more often. He suffered from pressure in the gastric region and from eructation for twenty-eight years. The hemorrhoids bled only slightly; the gums bled slightly; the region of the spleen was painful and tender. The spleen was distinctly enlarged. Curschmann [58] reported a second case in a man, aged 54, a merchant, and considered these cases, erroneously, as "nonsymptomatic pseudohemophilia," overlooking the many excellent reports on Osler's disease that have been published during the past thirty years.

Kromeke [59] discussed "Hereditary Hemorrhagic Thromboasthenia" and reported a number of cases. With one exception, a woman, aged 74, his patients showed fairly good platelet counts: 288,000 in a woman, aged 49, daughter of the first patient mentioned; 234,000 in her son,

54. Libert: Ann. de méd. et de chir. **1**:29, 1928-1929.

55. van Gilse, P. H. G., and Postma, C.: Nederl. tijdschr. v. geneesk. **1**:2648, 1928.

56. van Gilse, P. H. G.: Acta oto-laryng. **13**:525, 1929.

57. Osler, W.: Riforma med. **27**:57, 1911.

58. Curschmann, H.: Klin. Wchnschr. **9**:677, 1930.

59. Kromeke, F.: Deutsche med. Wchnschr. **48**:1102 (Aug. 18) 1922.

aged 19½; 110,200 in a second daughter, aged 47, and 109,300 in another daughter. Kromeke's cases were perhaps instances of Osler's disease. However, he reported them as cases of Frank-Glanzmann's "hereditary hemorrhagic thromboasthenia."

Schoen[60] (1930) reported two cases. A man, aged 56, suffered from profuse epistaxis since earliest childhood. Numerous telangiectasias were present on both cheeks, the left portion of the upper and lower lips, the ears, nose, chin, scalp, palate and tongue; there were isolated spots on the chest and the abdomen. The spleen was barely palpable. Varicose veins were seen on both legs. The second patient, a woman, aged 54, the sister of the first patient, had epistaxis since childhood. In 1917, she had pelvic hemorrhages, which ceased after

Fig. 5.—Telangiectasias with exophthalmic goiter. (Hyde: Brit. J. Dermat. **21**: 33, 1908.)

sixteen irradiations. In 1926, she vomited blood which she had swallowed. She had occasional hemorrhages of the lips while eating. She had telangiectasias on the cheeks, lips, neck, chest, left lower eyelid, ears, tongue, hard palate and nasal septum. She had dilated veins on the hands and varices of the legs.

Audry[61] (1920) reported a family in which familial hemorrhagic telangiectasia occurred in fifteen cases during four generations.

Baroux published a paper on the heredity of nevi in certain families, and in one of the families the records went back to the fifteenth century. In forty-one members of this family there were nevi situated at definite points, which were always the same.

60. Schoen, R.: Arch. f. klin. Med. **166**:156, 1930.

61. Audry, J.: Rev. de méd. **21**:22, 1911.

Mracek [62] (1904) expressed the belief that telangiectasia and nevus vasculosus are usually congenital dilatations of the capillaries and small blood vessels of the skin.

Raff and Rosenbaum believed that the senile angiomas of the skin are found exceedingly frequently in advanced age and have no etiologic connections with carcinomas.

Artom and Fornara [63] (1925) discussed telangiectasia vasoparalytica sistematizzata and reported a case of telangiectasia in a boy, F. Achille, aged 11. No hemorrhages were mentioned.

Marchisio [64] (1929) reported a case of purpura annularis telangiectodes de Majocchi in a young man, aged 26. The hips and the legs were involved nearly symmetrically. No tuberculosis was present.

Morawitz [65] (1930) discussed the "hemophilia problem" and reported a case of Wilebrand's pseudohemophilia in a boy, aged 14, who had been a bleeder since childhood. He suffered from hemorrhages into the joints and other parts of the body, hematuria and epistaxis. He had a large number of petechiae. The thrombocytes numbered 480,000. The coagulation and bleeding time were usually prolonged; but occasionally the coagulation time was normal and even shortened. This case, according to Morawitz, resembled hemophilia as well as thrombopenia, and was more like the case reported by Wilebrand than Wittkower's case. Lopis' peroral administration of vitamins A, B, C and D in combination with 20 cg. of calcium phosphate in lactose was used daily for three weeks, but without much effect. In a case of true hemophilia, however, Morawitz was able to reduce the coagulation time from one hundred and thirty minutes to from eight to eleven minutes after treatment.

Stadelmann [66] (1913) discussed "rare forms of gastro-intestinal hemorrhages" and reported cases of fatal hemorrhage due to numerous dilated veins (varices) of the stomach, of idiopathic origin and also cases showing varices of the intestines.

Vulpian's [67] patient (1886), a young man, aged 30, died of profuse epistaxis. He frequently bled from the nose, and after the age of 17, he bled from the gums. He had ecchymoses of the ears and the fingers. The spleen was at least double the normal size, but was not tender on percussion. Vulpian reported this case as an instance of hemophilia.

62. Mracek, F.: Atlas und Grundriss der Haut-Krankheiten, Munich, J. F. Lehmann, 1904.

63. Artom and Fornara: Systematized Vasoparalytic Telangiectasia, Gior. ital. di dermat. e sif. **66**:73, 1925.

64. Marchisio, L.: Gior. ital. di dermat. e sif. **70**:892, 1929.

65. Morawitz, P.: Hämophilieprobleme, Therap. d. Gegenw. **71**:1, 1930.

66. Stadelmann, E.: Berl. klin. Wchnschr. **1**:825, 1913.

67. Vulpian: Rev. de méd. **6**:153, 1886.

Vidal[68] (1880) did not mention hemorrhages in the report of his case of "symmetrical and generalized accidental telangiectasis," in a woman, aged 31. There were many permanent red spots on the forearms, wrists, arms, chest and neck, the backs of the hands, the lumbar and dorsal regions, and on the thigh and foot. They seemed to develop after an attack of chronic urticaria. She had many dark red and purplish spots on the face; they disappeared on pressure. Hyperesthesia of the affected regions was noted.

Blaschko[69] (1899) reported a case in a girl, aged 17, with severe telangiectasias of the head, the face and the trunk, "originating from a nevus on the right side of the abdomen." She suffered from hemorrhages from the urethra in her seventh and fourteenth years.

Fig. 6.—Bilateral telangiectasias of the trunk with epistaxis and rectal bleeding. (Fox: Brit. J. Dermat. **20**:145, 1908.)

Brocq (1904) discussed telangiectasia and its three classes, but did not mention hemorrhages of a familial type.

Hoffmann (1927) reported the case of a patient who had telangiectasias since the third year and in whom the condition had spread since the thirteenth year. The patient had syphilis and parenchymatous keratitis. Hemorrhage was not mentioned.

Terrien and Prelat[70] (1909) reported a case in a child in whom telangiectasias developed at the age of 3 months, on the face and the limbs. There were many small brownish pigmented spots on the trunk,

68. Vidal, E.: Bull. et mém. Soc. méd. d. hôp. de Paris **81**:186, 1880.
69. Blaschko: Monatschr. f. prakt. Dermat. **28**:451, 1899.
70. Terrien and Prelat: Bull. Soc. de pédiat. de Paris **9**:370, 1909.

a small pigmented nevus on the internal surface of the right knee and a larger one in the median line between the shoulders. There was evidence of thyroid insufficiency and bilateral cataracts.

Bonhomme de Montaigut [71] (1882), in his contribution to the study of epistaxis due to nasal varices, failed to mention telangiectasias, or the occurrence of familial types of nasal hemorrhages.

Two of the patients with Osler's disease mentioned by Erdheim [72] (1929) are believed to have died from the repeated hemorrhages.

Apert (1907), discussing idiopathic familial hematuria, stated that this condition was definitely established by the cases of Atlee [26] and of Guthrie.[8] Atlee saw three sisters, all with recurrent hematuria. Guthrie reported recurrent hematuria at irregular intervals since early life in twelve members of the same family.

Mention must be made of the case reported by Bennecke [73] (1906) in a man, aged 52, who died of tuberculous meningitis; at autopsy, telangiectatic lesions were found throughout the gastro-intestinal tract, on the lower lip and in the esophagus, stomach, intestines and rectum. The tongue and the pharynx were free from these spots. Bennecke expressed the belief that fatal hemorrhages may occur from such lesions. He mentioned reports by Sommer, Neelsen and Tierfelder. He claimed that these phlebectasias and telangiectasias are due to defective development of the muscular and elastic parts of the vessel walls. He stated that in some of the cases in the literature the phlebectasias, particularly of the esophagus, were the cause of fatal hemorrhage. Among these cases two have been in children. For the most part the phlebectasias have not caused symptoms.

Mantchik [74] (1922) reported a case of tracheal pseudo-hemoptysis (nontuberculous) in a man, aged 48, who bled from a telangiectatic spot on the anterior surface of the trachea at the level of the second ring. He was able to collect about ten cases of pseudo-hemoptysis or tracheal hemorrhage (nontuberculous).

Avellis reported a case of tracheal phlebectasia and hemorrhage (which he thought was due to chronic constipation). Perhaps some of the "monosymptomatic" (hemoptysis only) "abortive" tuberculous cases of Bard were cases of nonpulmonary hemorrhage from tracheal phlebectasia, or from telangiectasias in the finer bronchi, or perhaps they were similar to Libman and Ottenberg's [24] cases of familial hemoptysis.

71. Bonhomme de Montaigut: Contribution à l'étude de l'épistaxis, varices nasales, Paris, 1882, no. 142.

72. Erdheim, S.: Brit. J. Dermat. **41**:55, 1929.

73. Bennecke: Virchows Arch. f. path. Anat. **184**:71, 1906.

74. Mantchik, H.: Schweiz. med. Wchnschr. **52**:949, 1922.

Mere mention need be made here of the reports by Steiner and Voerner (1909), Goldstein [2] (1921, 1922, 1930 and 1931 [74a]), Petry [75] (1914), Uiberall [75a] (1930), Hicks and Knox [75b] (1931), Bottema [75c] (1930), Földvári [75d] (1930), Kindler [76] (1929), Romme [77] (1909), Rosenberg (1898), Kalischer (1901), Pollitzer, Pasini, Ullmann [40] (1930 and 1931), Du Castel and Baudouin [78] (1899), Curtius [79] (1928), Armand (1905), Duroziez,[80] Rendu [10] (1896), Laffont [49] (1909), and Miescher,[81] who, in his paper on "Essential Telangiectases and Some Observations on the Pathogenesis of Telangiectases," discussed the subject thoroughly.

Gastou [82] (1894) reported a case in a man, aged 45, who had generalized cutaneous vascular dilatations and suffered from general syphilitic pseudoparalysis. His youngest daughter had vascular dilatations. The father, daughter and all the paternal ascendants had red hair and a high facial color. The vascularization in both cases was at first localized; it became generalized in the father at the time of cerebral disturbances in the form of left-sided hemiplegia, and in the daughter after a confinement. The man had telangiectasias on the limbs, chest and back. Hemiplegia occurred at the age of 23, and cleared up after two months. The young woman had telangiectasias on the hands, from which they spread generally. Gastou expressed the belief that these cutaneous vascular dilatations may be the result of a vasomotor paralysis through congenital, hereditary or acquired modification of the vascular vasomotor centers, and he proposed to designate them, until their nature is better known, as generalized vasomotor telangiectasias.

Kopp's [83] patient (1897) was a young man of 19, who had many telangiectasias on the scrotum, the lower extremities and the trunk that

74a. Goldstein, H. I.: Multiple Hereditary Telangiectasia, Arch. Dermat. & Syph., to be published.

75. Petry, H.: Zur Kenntnis und Bedeutung des Nasenblutens im späteren Kindesalter, Berlin, Götting, 1914.

75a. Uiberall, H.: Hauthämangiomen, Ztschr. f. Neurol. u. Psychiat. **124**:863, 1930.

75b. Hicks and Knox: New York State J. Med. **31**:687 (June 1) 1931.

75c. Bottema, C. W.: Nederl. tijdschr. v. geneesk. **74**:5560 (Nov. 8) 1930.

75d. Földvári, F.: Zentralbl. f. Haut- u. Geschlechtskr. **35**:338, 1930-1931.

76. Kindler, W.: Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres **27**:369, 1929.

77. Romme, R.: Presse méd. **17**:293, 1909.

78. Du Castel and Baudouin: Bull. Soc. franç. de dermat. et syph. **10**:432, 1899.

79. Curtius: Klin. Wchnschr. **7**:2141, 1928.

80. Duroziez: De l'épistaxis rheumatismale et cardiaque, Tribuna med **13**:31, 1880.

81. Miescher: Arch. f. Dermat. u. Syph. **127**:791, 1919.

82. Gastou, P.: Bull. Soc. franç. de dermat. et syph. **5**:71, 1894.

83. Kopp: Arch. f. Dermat. u. Syph., January, 1897, vol. 38.

gave rise to unpleasant and protracted hemorrhages which alarmed the patient. Apparently no similar condition was observed in the family.

Emile-Weil (1926) reported a case in a woman, aged 36, who had telangiectasias of the face, lips, tongue, thorax and abdomen. She had frequent attacks of epistaxis and bleeding from the gums. She had severe varicose veins of the legs. Another patient, aged 43, had frequent epistaxis and hemorrhages from angiomas of the tongue and the ears. Two sisters bled from angiomas on the nasal and buccal mucous membrane and the ears. The patient's paternal uncle bled from the nose; his daughter had angiomas of the face and had hemorrhages from the nose, the tongue and the ear. The paternal grandfather of the patient, her father, brother, two sisters, uncle and cousin all had hemorrhages.

Kofler's [84] patient (1908), a man, aged 50, bled repeatedly from the lips and the nose. His mother and brother suffered similarly. There were spots on the face, lips, mouth, nose, ears, back of the scalp, extremities and trunk, the turbinals and one on the lower left eyelid. Many small telangiectasias were present on the tongue, the gums, the hard and soft palate, the posterior wall of the hypopharynx and on the right arytenoid cartilage. These lesions existed since early childhood. Kofler stated that hemorrhages from the lesions on the posterior wall of the pharynx and in the larynx might be confused with true hemoptysis. He erroneously considered his two cases as nevus Pringle, instead of Rendu-Osler-Weber's disease or heredofamilial angiomatosis (Goldstein).

Flandin and Soule's patient (1929), a woman, aged 54, bled profusely from the nose. She had hereditary hemorrhagic angiomatosis on the cheeks, chin, tongue and fingers. The bleeding time and coagulation time were normal.

Schwartz' [15] patient (Aug., 1925), a woman of 49, had severe nosebleed and hemorrhages from the tip of the tongue and from the tip of the right little finger. Her mother died of frequent, almost uncontrollable nasal hemorrhages. The patient had telangiectasias on the tongue, the lips, the hard and soft palates, the nasal mucosa, the conjunctivae, the ears, cheeks, hands and fingers and a few on the trunk.

Mekie's patient [85] (1927), a man, aged 38, had advanced tuberculosis and a long history of recurring epistaxis. He had numerous telangiectasias on the lips, nose, cheeks, tongue, gums, soft palate, penis and the dorsum of the glans. Eight others in his family had the same condition. One of the affected cousins died at the age of 28 from a ruptured vessel in the brain.

Brown [86] commented on a case in a woman about to come into labor, "a partial bleeder," who had almost uncontrollable hemorrhage in her

84. Kofler: Wien. klin. Wchnschr. **21**:570, 1908.

85. Mekie, E. C.: Brit. M. J. **1**:23, 1927.

86. Brown, H. A.: Treatment of "Hemophilia" During Parturition, J. A. M. A. **93**:478 (Aug. 10) 1929.

first confinement nine years previously. She did not bleed abnormally following the extraction of teeth or when she cut or scratched herself. Her father had pronounced "hemophilia." Brown could not explain why in his case the hemophilia was not sex-bound. Perhaps his cases were instances of Rendu-Osler-Weber's disease, and not hemophilia. No platelet count or bleeding and clotting time was given. The amount of calcium in the blood is not mentioned.

Time will not permit the discussion of cases reported by Apert,[30] Balph,[87] Henle,[25] Hurst,[27] Van der Zande [88] (pseudohemophilia, 1923), Hutchinson [89] (1885), Glanzmann [90] (1918), Hess [91] (1916), Buckman [92] (1928), Giffin [48] (1928), Little [93] (1928), Rothman and Nixon [94] (familial purpura hemorrhagica, 1929), McClure and Ellis [95] (hemangi-

Fig. 7.—Telangiectasia of the face. (Osler: Quart. J. Med. **1**:55, 1907.)

omas of the intestine, 1930), Ebert and Nomland (1930), Nicholas, Lebeuf and Michel (1930), Arnold [96] (telangiectatic granuloma of the

87. Balph, J.: Boston M. & S. J. **197**:1177, 1927.

88. Van der Zande, F.: Nederl. tijdschr. v. geneesk. **1**:544, 1923.

89. Hutchinson: Pedigree of Disease, New York, William Wood & Company, 1885, p. 101.

90. Glanzmann, E.: Jahrb. f. Kinderh. **88**:1, 1918.

91. Hess, A. F.: Hemophilia, Arch. Int. Med. **17**:203 (Feb.) 1916.

92. Buckman, T. E.: Am. J. M. Sc. **175**:307, 1928.

93. Little, W. D., and Ayres, W. W.: Hemorrhagic Disease, J. A. M. A. **91**:1251 (Oct. 27) 1928.

94. Rothman, P. E., and Nixon, N. K.: Familial Purpura Hemorrhagica Without Thrombopenia, J. A. M. A. **93**:15 (July 6) 1929.

95. McClure, R. D., and Ellis, S. W.: Am. J. Surg. **10**:241, 1930.

96. Arnold, J.: Zentralbl. f. Gynäk. **54**:1189, 1930.

vulva, 1930), Alessandri [97] (thoracic cutaneous telangiectasis in tuberculous subjects, 1930), Mayou (multiple telangiectasias in the bladder and on the legs, profuse hematuria, and double optic neuritis due to hemorrhages, 1908), Ullmann [40] (telangiectasias in the skin, respiratory mucous membrane, urethra, rectum and liver) and the hemangiomas of the intestine reported by Kornmann (1913), Laboulbene (1872), Brown (1924), Paci (1882), Shillito [98] (1920), Winternitz and Boggs (1910), Roedelius (1923), Judd and Rankin [99] (1922), Tuffier (1913), Nicoll (1899), and others.

Pringle saw an instance of hemoptysis. East collected thirty-five families with 237 affected persons and added his own cases. Pollitzer (1899) in his "International Atlas of Rare Skin Diseases" called a case "nevus" as it occurred in early life showing telangiectasias all over the body.

It is important to remember that a number of instances have been reported of cerebral hemorrhages and hemiplegia in young people due to Rendu-Osler-Weber's disease (Goldstein [8] [1921], Mekie [85] [1927], Archer [100] [1927], Gastou [82] [1894] and others).

Serious and recurrent attacks of hematuria, hemoptysis and hematemesis have occurred in some cases. A number of fatal cases are on record, as a direct result of the severe recurrent hemorrhages from the nose (Erdheim, Goldstein, etc.).

Heredofamilial angiomatosis (Goldstein) or Rendu-Osler-Weber's disease must be diagnosed on the basis of (1) heredity; (2) telangiectasia in most of the cases, and (3) hemorrhages chiefly from the nose, tongue and lips, and telangiectasia of the face and fingers. A number of instances are on record of hemorrhages from the pharynx, lungs, stomach, bowel, kidneys, birth canal, brain, eyes and ears.

Those interested in this clinical entity may refer to my [101] papers on the subject in the ARCHIVES OF INTERNAL MEDICINE (1921), and in the *Medical Times* (1930), and to Gjessing's,[33] Steiner's [49b] and Weber's [102] papers.

Osler's disease is to be distinguished as a separate, distinct, clinical entity from purpura, leukemias, Lindau's disease, von Hippel's disease, familial purpura without thrombopenia, hemophilia, pseudohemophilia, afibrinogenia (Opitz and Frei [102a]), hemacelinosis (Rayer), hemo-

97. Alessandri, C.: Riv. di pat. e clin. d. tuberc. **4**:502, 1930.
98. Shillito: Pennsylvania M. J. **24**:421, 1920-1921.
99. Judd and Rankin: Ann. Surg. **76**:28, 1922.
100. Archer, B. W. C.: Lancet **2**:595, 1927.
101. Goldstein (footnote 2, first and second references).
102. Weber, F. P.: Lancet **2**:160, 1907.
102a. Opitz and Frei: Afibrogenia, Jahrb. d. Kinderh. **94**:374, 1921.

genia (Weil [102b]), aleucia hemorrhagica (Frank), anemias and deficiency diseases.

In 1908, James Galloway [39] reviewed Kelly's [6] cases and Osler's cases reported in 1906 (by Coe [4]) and 1907 (by Osler [5]), mentioned Weber's and Bligh's cases and concluded by saying "and we understand that at least one other case has been recently observed in London."

Gougerot and Meyer reported familial telangiectasia with pregnancy.

Földvári [103] (1930) reported instances of hereditary hemorrhagic telangiectasia, including the cases of a man, aged 35 years, his father, a sister and her son, aged 8 years.

Sellei [104] (1930) discussed thoroughly the subject of telangiectases, as did also the late T. Colcott Fox [11] (1908).

Fig. 8.—Telangiectasia of the lips, palate and tongue. (Osler: Quart. J. Med. **1**:55, 1907.)

Alessandri [97] (1930) discussed cutaneous thoracic telangiectasias in tuberculous patients.

In his monograph on "The Pedigree of Disease," Hutchinson [105] reported instances of familial epistaxis. One of two brothers suffering from epistaxis died of hemorrhage at the age of 15½ years after bleeding from the nose for two years. The paternal grandfather had severe epistaxis and gout.

102b. Weil, P. E.: Hemogenia, Presse méd., March, 1925, no. 52; July, 1922, no. 21.

103. Földvári, F.: Telangiectasia Haemorrhagica Hereditaria, Zentralbl. f. Haut- u. Geschlechtskr. **35**:338 (Nov. 20) 1931.

104. Sellei, J.: Telangiectases, Acta dermat.-venereol. **11**:205 (June) 1930.

105. Hutchinson, Jonathan: The Pedigree of Disease, in Medical and Surgical Monographs I, 1889; footnote 89.

In 1930, Ullmann [106] discussed extensively the subject of angiomatosis and referred to his original case of "multiple eruptive angioma of the face" [107] as being perhaps the first reported instance of "telangiectasia hereditaria hemorrhagica with hemorrhages," and antedating Rendu's report.[10] In 1895, Ullmann failed, however, to connect the angiomas and hemorrhages of the mucous membrane as a definite familial hereditary clinical entity; otherwise, this interesting disease might now be known as "Ullmann's hereditary angiomatosis." Ullmann [108] referred to his report in the "Festschrift" for Kaposi. He recorded the presence of telangiectases in the skin, respiratory mucous membrane, urethra, rectum and liver.

Other studies of hemorrhages and dyscrasias of interest are: Rayer [109] (1827), Rothman and Nixon [94] (1929, hereditary hemorrhagic thrombasthenia), Hutchinson [89] (1885), Kretz [110] (1930), Glanzmann [90] (1918), Rivière [111] (1640, hemacelinosis), and Hess [112] (1916).

Incidentally, Rivière [111] treated hemacelinosis (purpura hemorrhagica) long before Werlhof [113] (1775) described the condition.

Rayer [113a] said that the celebrated Rivière (1640) had treated hemacelinosis long before Werlhof devoted a few lines to the description of this disease in his well known collection. "Graff, in 1775 (Göttingen), published the first dissertation on this affection." Perhaps Rayer and others overlooked Werlhof's original Brunswick Dissertation of 1731 and his works of 1731 to 1745.[113b]

---

106. Ullmann, K.: Wien. klin. Wchnschr. **43**:1538 (Dec. 11) 1930.

107. Ullmann, K.: Arch. f. Dermat. u. Syph., 1895; footnote 40.

108. Ullmann, K.: Ueber einen Fall von Angiomatosis, Festschrift zu Ehren von Kaposi, Leipzig, 1900, p. 559.

109. Rayer, P. F. O.: Hemorrhagies cutanées et souscutanées, Traité des maladies de la peau, Paris, 1827, vol. 2, p. 143.

110. Kretz, J.: Die hämorrhagischen Diathesen, Leipzig, Franz Deuticke, 1930, p. 89.

111. Rivière: Praxis med. lib., xvii, C. 1, Paris, 1640.

112. Hess, A. F.: The Blood and Blood Vessels in Hemophilia and Other Hemorrhagic Diseases, Arch. Int. Med. **17**:203 (Feb.) 1916.

113. Werlhof, P. G.: Commercium Noricium ad Rei Medicae et Scientiae Naturalis Incrementum Institut, 1745; Original Dissertation, Brunswick, 1735; Opera Omnia, Hannover, 1775, vol. 2, pp. 615 and 748; Commericium Litterarium ad Rei Medicae et Scientiae, Nuremberg, 1732; Pauli Gottlieb Werlhofii Observata Medico-Practica, in Opere Periodico Commercium Litterarium ad Rei, Hannover, J. E. Wichmann, 1775, part 2, pp. 615 and 748; Morbus Maculosus Hemorrhagicus, in Opera Medica, Hannover, J. E. Wickmann, 1775, part 2, pp. 615 and 748.

113a. Rayer, P. F. O.: Diseases of the Skin, translated by Dickinson, London, J. & A. Churchill, 1833, p. 294.

113b. Werlholf, P. G.: Dictionaire des sciences médicales, in Biographie Médicale, Paris, Panckoucke, 1825, tome VII, p. 494.

De Havilland Hall [114] discussed various causes of epistaxis, particularly purpura, hemophilia, scurvy, chlorosis, malaria, pernicious anemia, etc., but did not mention telangiectasia or rheumatism.

Moormann (1829), Emele (1747), Morgenstern (1749), Arnin (1824), Stempel (1710), Cock (1822), Stephenson (1822) and Wolff (1883) wrote on purpura.

Schmelzer (1831), Immerman (1876) and Heffler wrote on "morbus maculosus haemorrhagicus Werlhofii."

Rendu [115] (1884) stated that epistaxis may occur in young persons who later are subject to piles and rheumatism. Phillips concluded that epistaxis occurs in young persons who already have rheumatism.

Fig. 9.—Telangiectasia of the face, lips and nose. (Osler: Quart. J. Med. **1**:55, 1907).

Phillips [116] spoke on "Rheumatism as a Cause of Epistaxis in Children" before the Harveian Society of London in 1902. Ewart and Guthrie discussed the paper.

Apert [117] referred to Atlee's and Guthrie's case reports. Atlee's patients were three sisters, all of whom suffered from attacks of hematuria. The family mentioned by Guthrie consisted of sixteen persons in two generations; twelve of the members (five males and seven females) had attacks of hematuria from birth, which recurred at irregular intervals. They did not have hemophilia and had never suffered

114. de Havilland Hall, F.: Westminster Hosp. Rep. **8**:1, 1893.

115. Rendu: Semaine méd. **4**:241 and 257, 1884.

116. Phillips, Sidney: Lancet, Feb. 15 and 22, 1902.

117. Apert, E.: Traité des maladies familiales et des maladies congénitales, Paris, 1907, p. 288.

from purpura, urticaria, erythema, oxaluria or cyanosis of the extremities. Only hematuria occurred.

Rothman and Nixon [94] discussed hereditary hemorrhagic thrombasthenia—familial purpura hemorrhagica without thrombopenia. They quoted from Hutchinson's paper on "Pedigree of Disease," and gave data on a schoolboy who had repeated and alarming attacks of epistaxis. The boy's elder brother had died of epistaxis of four days' duration. Their paternal grandfather had suffered much from gout, and their father at the age of 22 had had severe epistaxis. The history of inherited gout as a frequent cause for retinitis hemorrhagica, blood patches in the conjunctivae, cerebral hemorrhage and epistaxis is emphasized by Hutchinson. Rothman and Nixon's patient, a boy, aged 13, apparently had not had telangiectases in the nose and throat. Epistaxis, oozing from the gums and numerous ecchymotic spots were present over the entire body. Moderate oozing of blood for two days followed the extraction of a tooth. Coagulation of the blood was complete in five minutes.

Buckman's patients showed prolongation of both coagulation and bleeding time.

Giffin reported severe hemorrhagic disease occurring in four generations. Bleeding time and prothrombin time were prolonged. The platelets and coagulation time were normal.

Little and Ayres traced a family through five generations. Coagulation time and platelets were normal in two typical cases with prolonged bleeding time.

Rosenthal's [118] (1928) patients, a mother and son, suffered from "chronic thrombasthenic purpura;" the platelets were normal, and the bleeding time and coagulation time were prolonged.

Van der Zande [88] (1923) reported a similarly affected family.

Rayer [119] (1833), in his treatise on "Diseases of the Skin," discussed hemacelinosis, or spotted hemorrhagic disease of Werlhof, as an apyretic condition, starting with petechiae or red, violet or livid spots scattered over the surface of the body, and formed by blood effused into the substance of the skin or beneath this membrane. When hemacelinosis develops in a healthy subject, it is seldom preceded by premonitory symptoms, yet, it is occasionally preceded by epistaxis, hematemesis, hemoptysis, etc., or by other hemorrhages from the mucous membranes. In some subjects, intestinal, uterine, vaginal or vesical hemorrhages take place. Of all internal hemorrhages, epistaxis appears to be the most frequent in children, menorrhagia in women and pulmonary or intestinal

118. Rosenthal: J. Lab. & Clin. Med. **13**:303 (Jan.) 1928.

119. Rayer, P. F. O.: "Haemacelinosis," in Diseases of the Skin, translated by W. B. Dickinson, London, J. & A. Churchill, 1833, p. 289.

hemorrhage in men. In his "Traité des maladies de la peau" [120] under "Hemorrhagies" (pp. 503-547), Rayer discussed hemorrhages of the skin and mucous membranes; purpura hemorrhagica with epistaxis (p. 512) and with hemorrhage of the stomach (p. 513). He gave many references to the literature on hemorrhages and hemorrhagic diseases from 1640 to 1825. Glanzmann [90] reported in detail an unusual form of purpura in eight families; he called the condition "hereditary hemorrhagic thrombasthenia." Both sexes are affected. The disease is more often transmitted by females. Attacks of epistaxis and ecchymoses occur. The blood platelets are normal or increased. The coagulation and bleeding time are normal. Failure of the clot to retract normally is emphasized by Glanzmann. In many of the cases retraction of the clot was entirely absent or incomplete.

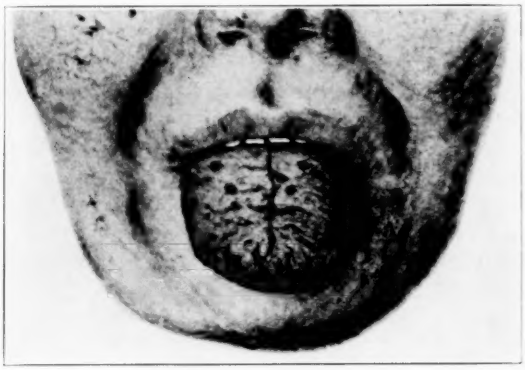


Fig. 10.—Telangiectasias of the tongue. (Steiner: Arch. Int. Med. **19**:194 [Feb.] 1907.)

Minot's two families were somewhat similar, but bleeding time was prolonged while platelets, coagulation time, clot retraction and a tourniquet test were normal. Repeated epistaxis occurred, apparently without nasal telangiectases. There was no abnormal bleeding after operations. Glanzmann emphasized the differential diagnosis of this condition from "Hämophilie und der hereditären hämorrhagischen Teleangiektasie" (pp. 128-136) and gave many references to the literature (pp. 138-141).

Hyde [121] (1908) discussed the occurrence of telangiectatic lesions of the skin occurring in subjects with exophthalmic goiter. He stated among the minor morbid conditions that may be encountered in cases

120. Rayer, P. F. O.: Traité des maladies de la peau, Paris, 1835, vol. 3.

121. Hyde, J. N.: Telangiectatic Lesions of the Skin Occurring in Graves' Disease, Brit. J. Dermat. **21**:33 (Feb.) 1908.

of exophthalmic goiter affecting the skin may be named pruritus, hyperhidrosis and hydrocystoma, erythematous flushing, scleroderma, myxedema and telangiectasis. While cutaneous telangiectasis is rare in cases of goiter (exophthalmic), Hyde reported four personal cases in women aged 57, 50, 43 and 24 years. He referred to papers by Barker (1907), Dore [122] (1900), Hyde and McEwen (1903), Nicol [123] (1900) and Létienne and Arnal [124] (1897).

Nicol [123] wrote on cutaneous hemorrhages and pigmentation in exophthalmic goiter.

Fox [11] reviewed the literature on "telangiectases" up to 1908 most exhaustively. He referred to the work on telangiectases by Besnier and Doyon,[125] Louis Brocq and Lanceplaine [126] (1904).

Hulke [127] (1876) described a case of general telangiectasis, most developed in the left half of the body and associated with abnormalities of the large blood vessels in the lower part of the left limb and in the neck. The condition began with a few nevoid specks in early infancy. Stryker reported (1927) a probable case of Goldstein's disease.

Crocker [128] reported the case of a girl who at the age of 7 years had a great number of dilated vessels. This condition began on the face, on the extensor aspect of the forearms and on the backs of the hands when she was 5 years of age; when she was 14 years of age the pathologic process was still increasing. In June, 1890, the lesions extended down the sides of the neck and on to the first phalanges. These "minute red points" and lilac-colored spots disappeared on pressure.

Sheild's [129] patient (1907) had a port-wine nevus of both hands and feet, which disseminated up the limb and slightly on the face and chin.

Hutchinson [130] (1858) found more than 150 nevi on the face, scalp, shoulders, body and arms of a boy aged 3 weeks.

Fox [131] (1883) reported a case of a girl 9 years old, with a large nevoid swelling between the shoulders, and on the trunk, left arm and right leg small congenital macules, varying in size from a pinhead to a finger-nail.

---

122. Dore: Cutaneous Affections Occurring in the Course of Graves' Disease, Brit. J. Dermat. **12**:353, 1900.

123. Nicol: Brit. J. Dermat. **12**:56, 1900.

124. Létienne, A., and Arnal, E.: Arch. gén. de méd. **7**:513, 1897.

125. Besnier and Doyon, in Kaposi: Maladies de la peau, Paris, vol. 2, p. 354.

126. Lanceplaine, R.: Étude sur les télangiectasies essentielles, Paris, 1904.

127. Hulke: Roy. Med.-Chir. Soc., Dec. 12, 1876.

128. Crocker: Atlas of the Diseases of the Skin, London, 1896, vol. 2, plate LXXI, fig. 1.

129. Sheild: Brit. J. Dermat. **19**:257 (July) 1907.

130. Hutchinson, J.: Lancet, Jan. 16, 1858.

131. Fox: Dermat. Soc. London, April 11, 1883.

Hutchinson [132] reported cases of infective angioma.

Fox referred to interesting cases reported by Francis, Augsburg (1903), Pollitzer (1898), Fordyce (1890), Majocchi (1896), Morris (1900), Dundee (1897), Gaucher and Crouzon (1902), Gilbert and Hirscher (1903), J. Galloway (1908), Morrow (1894), Levi and Delherm (1901), Levi and Lenoble (1896), Brocq (1897), Gastou (1894), Morny and Malloizel (1905), and many others.

Telangiectases symptomatic of disturbed general circulation are not infrequent, either from faulty myocardium or valves and sometimes from disease of the lungs, liver and spleen, according to Fox. He referred also to angiokeratoma or acrotelangiectasis. Several children in a family may be thus affected.

Fig. 11.—Telangiectasias on the face. (Steiner: Arch. Int. Med. **19**:194 [Feb.] 1917.)

Symmers [133] (1902) and Dubreuilh (1900) do not believe that angiomas of the skin bear any relation to malignant disease, as both conditions have an incidence in the later periods of life. Symmers expressed the belief that the senile angiomas and telangiectases are probably significant of some form of well marked arterial degeneration. Fox thought that this type must be placed with the essential telangiectases.

Anderson's patient [134] (1898), a man, aged 39, had many small angiomas on trunk and extremities; when he was 18 he had had rectal bleeding for five weeks. There was no family history of angiomas or epistaxis or personal history of nosebleed.

---

132. Hutchinson, J.: On Certain Forms of Angiomata Which Are Infective, Arch. Surg., London **11**:221, 1900, plate IX.

133. Symmers, Douglas: M. News, Dec. 27, 1902.

134. Anderson: Brit. J. Dermat. **10**:114, 1898.

Kendall and Hertz[135] (1912) reported cases of hereditary familial congenital hematuria (hemorrhagic nephritis) in one family in two generations. They included several of Guthrie's cases and also referred to Dickinson's (1875) and Atlee's (1901) reported cases. Their cases were later included in a report by Hurst (1923).

McClure and Ellis[95] of Detroit reported a case of hemangiomas of the intestine in a woman, aged 30 years. She had melena (tarry stools) frequently for ten years. For years she had had a large number of blood tumors on her skin. One had ruptured and bled profusely. In 1919, following influenza, she had copious hemorrhages from the uterus. Hematuria was noted on several occasions. She was treated for anemia in childhood. Her parents and several brothers and sisters were normal. No other members of the family had similar "blood tumors." No mention is made of nosebleed in the patient or patient's family. The patient had a large number of reddish or purplish-red "vascular tumors," varying in size from a pinhead to 1 cm. in diameter, scattered over the entire body, but chiefly on the back, buttocks and legs. Along the left lateral margin of the tongue was a hemangioma surrounded by dilated blood vessels. No mention was made of coagulation and bleeding time, blood platelets and blood calcium until after a three months' course of modified Sippy treatment and transfusions of blood; at this time there were 210,000 platelets; there was secondary anemia, and the coagulation time was twenty-six and one-half minutes (Howell tube). The bleeding time was normal. Before operation, the blood calcium was "within normal limits" and showed no increase after treatment with calcium lactate, injections of parathyroid extract-Collip and repeated transfusions of blood. At operation, it was found that the patient had similar vascular lesions on the wall of the stomach (anterior), the liver, duodenum, wall of the gallbladder, jejunum and ileum. The kidneys, appendix, tubes and ovaries were normal. Four months after operation, she died of hemorrhage from the bowel. She may have had some lesions in the mucosa of the bladder (hematuria). The capsule of the spleen was entirely covered by dilated blood vessels.

In 1930, Weber of London presented before the Section of Dermatology of the Royal Society of Medicine, a case of telangiectasia macularis eruptiva perstans, probably a telangiectatic variety of urticaria pigmentosa, in an obese woman, aged 60 years. He[136] discussed this condition in an article in the *International Clinics* in June, 1931.

Ebert and Nomland[137] (1930) reported a case of generalized telangiectasia in which the family history was unimportant. The

135. Kendall and Hertz: Guy's Hosp. Rep. **46**:137, 1912.

136. Weber, F. P.: Osler's "Telangiectasia Circumscripta Unversalis" and Urticaria Pigmentosa of Adults, Internat. Clin. **2**:131 (June) 1931.

137. Ebert, M. H., and Nomland, R.: Generalized Telangiectasia, Arch. Dermat. & Syph. **22**:346 (Aug.) 1930.

patient, a girl, aged 11 years, had had telangiectasia since birth, over the face, sternal region, left hand and torso. The soles, scalp and palms (except for the thenar eminence) were free. Becker considered this case generalized telangiectasia with mental inferiority and endocrine disturbance.

Gaucher and Crouzon (1902) described a case in a woman, aged 28, in whom, after vaginal hysterectomy, diffuse areas of telangiectases developed over the face, shoulders and lower extremities.

Fitz-Hugh [138] (1931) reported the following four cases of hereditary hemorrhagic telangiectasia with splenomegalia and hepatic enlargement with identical blood group 0 (Moss IV) and increasing intolerance to transfusion of blood resulting in posttransfusion jaundice (and death in two). The four patients were unrelated.

CASE 1.—Max G. was treated at the University Hospital, Philadelphia, in 1910, 1917, 1924, 1927 and from Dec. 20, 1929, to Jan. 18, 1930. He had recurrent epistaxis all his life; occasional hemoptysis and melena also occurred. Dr. Tucker, in 1924, found distinct telangiectases in the trachea and left bronchus on bronchoscopic examination, and Dr. Ravdin (1924) found lesions in the mucosa of the rectum proctoscopically (examined microscopically after biopsy). The patient also had telangiectases on the lips, face, nose, septum and tongue. Cystoscopy (1924) was negative for telangiectases. In 1917, Dr. Pepper first noted enlargement of the spleen; the patient suffered from several profuse hemorrhages from the nose and mouth which were interpreted as probably due to tuberculosis, although no tubercle bacilli were found. The patient died, and autopsy was performed.

CASE 2.—A woman, aged 46 (1927), presented typical hereditary telangiectasia (Rendu-Osler-Weber's disease). Examination on April 23, 1927, showed leukopenia with 4,000 white blood cells, 130,000 blood platelets and 2,500,000 red blood cells. The spleen was enlarged. In April, 1929, the liver was reported as enlarged. The patient died in December, 1929, but autopsy was not obtained.

CASE 3.—A woman, aged 40 (1924), suffered from recurrent epistaxis and occasional bleeding from "spots on her tongue." Four years previously she had severe melena which necessitated transfusion of blood. She had telangiectases on the tongue, palate, uvula, lips, cheeks, nose, forehead, neck, abdomen and under the nail-beds. The spleen was "readily palpable."

CASE 4.—A woman, aged 58 (July, 1929), presented a typical case of Osler's disease or heredofamilial angiomatosis (Goldstein), with recurrent epistaxis and an enlarged spleen and liver. Her son, 35 years of age, was treated by Dr. Houser of Philadelphia for violent epistaxis. Fitz-Hugh examined him, but his spleen and liver were not palpable.

Ullmann [40] had a moulage made of the face of a healthy woman, aged 40, born of healthy parents, who came to Hebra's clinic in 1892, presenting a number of roundish purplish angiomas on the face, varying in size from a hemp-seed to a small pea, and several small pigmented

138. Fitz-Hugh, T., Jr.: Am. J. M. Sc. **181**:261 (Feb.) 1931.

hairy moles on the neck. The angiomas did not wholly disappear on pressure. In 1894, a few more angiomas had developed, and in 1895 many more, some becoming septic and breaking down with enlargement of related glands. Histologically, the growths were cavernous angiomas, with thinning and stretching of the epidermis and flattening of the papillary layer. The larger vessels contained an organized thrombus. In 1898, the patient had pneumonia of the left lung and evolution of large lesions on the body, some as big as a small apple. A few suppurated with streptococci present. These large growths were found not to be sarcomatous, but cavernous angiomas. Several burst and bled freely. In 1899, lesions began to develop on the tracheal and bronchial mucous membrane and caused hemoptysis. Finally, the patient died from a second attack of pneumonia, and at the autopsy angiomas were found in

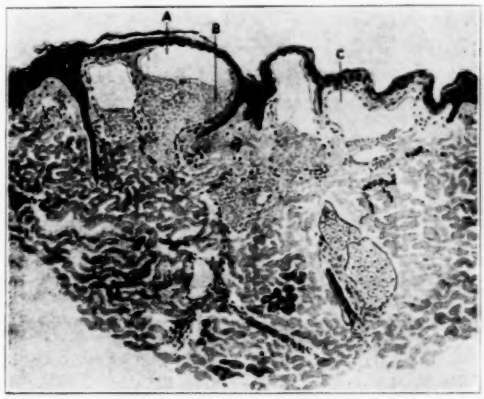


Fig. 12.—Section of telangiectasias from the back. *A* indicates serum; *B* blood corpuscles; *C*, dilated capillaries. (Fox: Brit. J. Dermat. **20**:145, 1908.)

the skin, respiratory mucous membranes, rectum, urethra and liver. The liver and spleen were atrophied.

Kopp [83] published a case of a young man, aged about 19 years, who about eighteen months before he came under observation noticed small red spots on the scrotum and scattered over the lower extremities, and later, similar lesions on the trunk and upper extremities. About thirty small red nodules of irregular surface were present; they began as punctae. The internal organs revealed nothing abnormal, and the history did not reveal any similar condition on either parental side.

Mandelbaum [139] (1882) described a case of a man, aged 30, of a healthy family, who had syphilis at 17; at 21 a fine vascular network

139. Mandelbaum, W.: Vrtljschr. f. Dermat. u. Syph. **17**:186, 1882.

developed on the face, and then on the neck, chest and limbs disseminated purplish nodules developed varying from a pinhead to a linseed in size. In places they were grouped, and in places almost confluent. There was no clue to the cause.

Bligh's [140] (1907) case is an illustration of the fact that troublesome hemorrhage may arise from these angiomas.

There are about a half dozen cases reported in the literature of enlargement of the spleen and liver in the advanced and more serious cases of Goldstein's heredofamilial angiomatosis ("Goldstein's disease") (telangiectasia) with familial hemorrhages (Rendu-Osler-Weber's disease).

It also appears that in cases with type IV, Moss (group 0) blood, the patients are much more prone to be intolerant to transfusions.

I recently (March 25, 1931) saw such a case, through the courtesy of Dr. A. A. Sussman, at the Sinai Hospital, Baltimore. A woman (Mrs. B. S.), aged 42, had severe anemia, ascites, enlarged spleen and liver, many telangiectases on the tongue, palate, tips of the fingers and nasal septum, and a history of recurrent hemorrhages since childhood. She developed severe reactions to transfusions of blood. There were, I believe, seventeen or eighteen members of her family who suffered from epistaxis and other hemorrhages, including her mother, grandfather and great grandfather. This was a typical case of heredofamilial epistaxis with angiomatosis. I also saw the patient's mother.

CONCLUSIONS

1. There are on record in the entire available medical literature of the world about ninety or ninety-five families and about 500 or 550 persons affected with this condition.

2. Rendu-Osler-Weber's disease is a definite clinical entity, recognized as such, for nearly thirty-five years (Rendu, 1896; Gastou, 1894; Osler, 1901; Weber, 1902).

3. This disease may occur with variations as to hemorrhages and telangiectasias. However, epistaxis of the familial type and the occurrence of multiple hemorrhagic (hereditary) telangiectasias on the face, in the nasal septum and in the mouth are the most common manifestations.

4. A discussion and a review of the literature on hemorrhages in Rendu-Osler-Weber's disease is given in this paper.

5. In the later stages of this disease, the spleen may be enlarged (Osler, Curschmann, Schoen, Giffin, Roles, Fitz-Hugh, Jr., Goldstein).

6. Heredity, hemorrhage and telangiectasia are the three cardinal points for diagnosis.

---

140. Bligh, W.: Lancet **1**:506, 1907.

7. Reported instances of "familial epistaxis" (with or without telangiectasia), "familial hemoptysis," "familial hematuria," "familial gastrostaxis" and familial (hereditary) telangiectasia are different forms of Rendu-Osler-Weber's disease or Goldstein's heredofamilial angiomatosis with recurring familial hemorrhages.

8. This condition is not sex-bound; it occurs in both sexes, and is transmitted by both sexes. The coagulation of the blood and the bleeding time, the blood platelets, blood calcium and fragility of the red blood cells are normal. Secondary anemia of greater or less degree may be present. Kinetocytes (Edelmann) in the blood of these patients have not yet been studied. They were greatly increased in thrombopenic purpura, in the case of a young woman I studied with Edelmann in Vienna.

9. Atavism (Fitz-Hugh and others) is a factor in the heredity of this disease.

10. As the condition is one of heredity and is due to congenital weakness and defect of the blood vessel system, no cure, as such, is possible. Treatment is only possible for the hemorrhages, the approachable bleeding points and the secondary anemia. Transfusions of blood and the use of radium and roentgen rays over the spleen and the bleeding areas may be tried, together with local measures (cautery, styptics, etc.). Liver, parathormone, calcium, iron and arsenic have been used.

1425 Broadway.

ISOLATED CONGENITAL DEXTROCARDIA

REPORT OF TWO CASES WITH UNUSUAL ELECTROCARDIOGRAPHIC FINDINGS; ANATOMIC, CLINICAL, ROENTGENOLOGIC AND ELECTROCARDIOGRAPHIC STUDIES OF THE CASES REPORTED IN THE LITERATURE

S. S. LICHTMAN, M.D.
NEW YORK

Concluded from p. 717.

ROENTGEN OBSERVATIONS

The roentgenogram serves to disclose extracardiac factors for the displacement of the heart. The position of the mediastinal contents and the nature of the shadows in the pulmonary fields indicate whether the displacement is the result of traction of a fibrotic process, tumor or fluid. Mobility of the diaphragm and change in the position of the apex with change of posture signify the absence of pleuropulmonary and diaphragmatic adhesions.

In the uncomplicated mirror-picture dextrocardia, the contour of the heart, with definite apex pointing to the right, is the mirror-image of the normal situation and identical with the heart in situs inversus. The course of the aortic arch, however, varies crossing the right bronchus more frequently than the left. In complicated cases the apical region is rounded and the normal cardiac contour modified by the hypertrophy of the right side of the heart, rarely the left, so that distinction between the two types of isolated dextrocardia cannot be made. Nagel's case demonstrates that with the x-rays a mirror-image shadow may be obtained with normal relationship of the chambers. Nagel demanded for diagnosis of isolated dextrocardia a definite apex to the right, which condition can be expected only when the right ventricle alone forms the apex of the heart. This anomaly was found in only 4 cases with necropsy and good roentgenograms (Nagel; Morgan; Mautner and Löwy; Rösler, Spitzer).

In the x-ray plate and fluoroscopic examination of every case of dextrocardia, the course of the arch of the aorta in relation to the right or left bronchus, of the descending aorta in relation to the vertebral

column, the contents of the first and second oblique positions of the chest and relative height of the leaves of the diaphragm should be noted.

Few observations in the oblique position have been recorded in isolated dextrocardia. In his case, Bahn recorded visualization of the ascending aorta and the arch of the aorta in the first oblique position. The first oblique in Botteri's case gave a normal appearance, the auricular contour was visible in the second oblique while the retrocardiac space was seen in the frontal view indicating torsion of the heart. In the case of Gautier and Coeytaux, likewise associated with torsion of the vascular pedicle, the first oblique position was also clear. In Strothmann's case of isolated dextrocardia with inversion of the chambers and transposition of the vessels, the aorta was visible in the retrocardiac space in the first oblique position; in the second oblique position, the aorta is seen to rise from the right ventricle, going from left to right. In both my cases, although different in type, the retrocardiac space was observed in the second oblique position; the arch of the aorta could not be traced in the second case.

The position of both leaves of the diaphragm in relation to dextrocardia was first noted by Wehn (1882), who concluded that the liver and the heart or blood vessels or the relationship of the lungs determined the normal elevation of the right leaf. Vehsemeyer in the first roentgenographic study of dextrocardia noted elevation of the left leaf of the diaphragm and connected the depression of the right leaf of the diaphragm with the dextrocardia. Nagel, in his case, also noted the depression of the right leaf of the diaphragm. Stoerk and Lenk favored the concept that the elevation of the left leaf of the diaphragm is responsible for the displacement of the heart to the right. In Botteri's and Gautier and Coeytaux's cases, this elevation of the left leaf of the diaphragm (not true eventration) has been interpreted as a possible cause of the displacement of the heart to the right with torsion of the vascular pedicle. Aimé stated that the cupola juxtacardiaque is always the lowest even when it is suprahepatic. Mandelstamm and Reinberg studied this point in their cases, and concluded therefrom that the heart rather than the liver determines the difference in the heights of both leaves of the diaphragm. Knape's case of inversion of the abdominal organs, with the apex of the heart pointing to the left and elevation of the right leaf of the diaphragm, supports this point of view. Rösler, in his intensive study, arrived at the same conclusion. In only two instances did he find the normal relationship of the diaphragm in dextrocardia (Fulchiero and Bruno, roentgeno-

graphic diagram, and Morgan, roentgenographic description); in all others, the right leaf was lower. In four instances, the position was verified by necropsy (in Lucchi's case both were even; in Ratner, Abbott and Beattie's, and in Löwenthal's cases the right was lower, and in the case of Rösler and of Spitzer the left was deeper). The roentgenographic observation made during life is undoubtedly the more accurate. In my series the position of the diaphragm was recorded in 49 cases:

Right leaf lower (35 cases): Nagel; Foggie; Ratner; Abbott and Beattie (post mortem); Rösler; Spitzer (roentgenogram, right lower; post mortem, left lower); Vehsemeyer; Crispino; Neumann; Geissler; Giovannini; Botteri; Moffett and Neuhof?; Clerc and Bobri; Duval; Weinberger, case 1; Mandelstamm and Reinberg, cases 5, 6, 7a, 7b, 9; Gorter, cases 1 and 4; Capon and Chamberlain; Gautier and Coeytaux; Lenk; Colvin; Prendergrass; Aimé; Milani; Loben; Rösler, cases 1, 4 and 5; Lichtman, cases 1 and 2.

Left leaf lower (3 cases): Lochte (post mortem only); Morgan (description of roentgenogram); Fulchiero and Bruno.

Both leaves of equal height (11 cases): Mautner and Löwy; Biedermann; Leo; Sheffield; Vaquez and Donzelot, case 1; Gorter, cases 4 and 5; Krestin; Strothmann; Rösler, cases 3 and 7.

Roentgenographic examination further demonstrates the position of the liver in the right hypochondriac region; with the aid of carbon dioxide gas or barium sulphate, the roentgen rays show also the normal position of the stomach as well as that of the entire intestinal tract. The position of the gallbladder is demonstrated by cholecystography.

Bronchography may be attempted to diagnose transposition of the bronchial tree and lungs, although normal variations in the distribution of the bronchi and pulmonary lobes make this procedure of doubtful value.

Roentgenographic examination was made in 76 cases of the series. Plates or descriptions are recorded in 46 cases. In table 2 are recorded 33 cases with both roentgenographic and electrocardiographic studies. The findings in all cases in which roentgenograms were made are enumerated as follows:

Mirror-picture roentgenogram (9 cases):
Necropsy: Nagel; Morgan; Mautner and Löwy.
Clinical: Geissler; Capon and Chamberlain; Fulchiero and Bruno; Mandelstamm and Reinberg, cases 8 and 9; Rösler, case 5.
Mirror-picture roentgenogram with slight variation (3 cases):
Necropsy: Rösler, Spitzer.
Clinical: Vehsemeyer; Vaquez and Donzelot, case 2.
Atypical roentgenographic cardiac shadow (22 cases):
Necropsy: No case.
Clinical: Leo; Ziemsen and Rieder; Neumann; Sheffield; Botteri; Indemans; Weinberger, case 1; Gorter, cases 4 and 5; Krestin; Loben; Lenk; Milani; Mandelstamm and Reinberg, cases 5, 6, 7, 7a, 7b; Rösler, cases 2, 3, 4, 7.

Mirror-picture heart and left aorta (2 cases):
Necropsy: Mautner and Löwy.
Clinical: Fulchiero and Bruno.
Mirror-picture heart with slight variation and left aorta (2 cases):
Clinical: Vaquez and Donzelot, case 2; Gorter, case 1.
Mirror-picture heart with apparent left aorta (1 case):
Clinical: Colvin.
Mirror-picture heart and right aortic arch (4 cases):
Necropsy: Nagel.
Clinical: Geissler; Mandelstamm and Reinberg, case 9; Rösler, case 5.
Mirror-picture with probable right aortic arch (1 case):
Clinical: Capon and Chamberlain.
Mirror-picture with slight variation and right aortic arch (1 case):
Necropsy: Rösler and Spitzer.
Atypical (not mirror-image) heart and normal left aorta (11 cases):
Clinical: Ziemssen, Rieder; Weinberger; Loben; Lenk; Mendelstamm and Reinberg, cases 5, 6, 7 and 7b; Rösler, cases 3, 4 and 7.
Atypical (not mirror-image) heart and probable left aorta (2 cases):
Clinical: Leo; Gorter, case 4.
Atypical (not mirror-image) heart and definite right aortic arch (3 cases):
Clinical: Krestin; Mandelstamm and Reinberg, 7A; Rösler, case 2.
Aortic arch and descending aorta:
Right aortic arch:
Roentgenogram: 17 cases, 1 case?; 7 with left descending, 10 with right.
Necropsy: 6 cases.
Left aortic arch:
Roentgenogram: 28 cases.
Necrosy: 11 cases.
Physical signs: 1 case (dilated).
Right descending aorta:
Roentgenogram: 19 cases (1 case?).
Necropsy: 5 cases (1 case abdominal aorta).
Left descending aorta:
Roentgenogram: 31 cases (1 case?).
Necropsy: 11 cases.
Physical signs: 1 case (palpation of abdominal aorta).
Transposition of great vessels (12 cases):
Necropsy: 11 cases.
Roentgenogram: 1 case.
"Corrected transposition":
Necropsy: 3 cases.
Persistent right aortic arch:
Necropsy: 4 cases.

A practical summary of the roentgenographic findings may be stated thus:

With a mirror-picture heart shadow, a right aorta is found in relation to a left as 4:2; or 6:5 if probable cases are included.

With an atypical (not mirror-image heart shadow), the right aorta is found in relation to the left as 11:3; or 13:3 if probable cases are included.

Therefore, in the majority of cases (4:2) of isolated dextrocardia with inversion of the chambers there is a right aorta, while in the type with normal relationship of chambers there is a left aorta in the far greater number (11:3). A comparison between the postmortem and roentgenographic courses of the aorta in mirror-picture dextrocardia and situs solitus dextrocardia would indicate that there is less divergence between the roentgenographic and postmortem evidence in situs solitus dextrocardia than in mirror-picture dextrocardia.

ELECTROCARDIOGRAPHIC OBSERVATIONS

Mirror-Picture Dextrocardia.—Complete inversion of lead I is accepted as evidence of inversion of the chambers of the heart occurring in the mirror-picture dextrocardia of complete situs inversus or in the isolated type (Waller and Nicolai, confirmed by Wohrizek, Hoke, Owen, Einthoven, Fahr and de Waart, de Castro). This inversion of the curve gives evidence not only of transposition of the chambers proper, but of the conduction system. The atrium excitation runs from left to right. The excitation in the papillary system runs so that its beginning is nearer the right arm than the left, and at the end of excitation it spreads more to the left than to the right, as it does in the normal (Nicolai). It is readily understood, since in the first lead the transverse component predominates and it is the only symmetrical lead, why this lead alone is affected by transposition of the chambers of the heart, being the equivalent of the reversal of the poles of this lead.

To Samoiloff belongs the credit for pointing out that leads II and III remain upright although they interchange (confirmed by Lewis, Neuhof, Hoffmann, and others). In these leads, whatever the situation of the cavities, the direction of the current does not change save that lead II which normally follows the electrical axis of the heart is replaced in this respect by lead III. A schematic representation of the explanation for the interchange of leads II and III is given by Samoiloff.

Dextrocardia with Normal Arrangement of Chambers.—In dextrocardia with normally related chambers lead I remains upright, and when uncomplicated leads II and III are interchanged, and there is evidence of right ventricular predominance.

Electrocardiographic observations were made in 34 cases of the series (table 2). In 4 cases postmortem studies were also made (table 1); there was agreement between the findings at necropsy and those obtained in the electrocardiogram in two cases (Bahn, Pol; Biedermann). The original curves must be consulted for the presence of

right or left ventricular predominance. Some types of congenital malformation tend to show left ventricular predominance (conus, aortic or isthmus stenosis and cases with extremely small right ventricle, i. e., tricuspid stenosis). Seven cases were incomplete in the ordinary details of the electrocardiogram (Stoerk; Moffett and Neuhof; Boruttau and Stadelmann; Weinberger, cases 1 and 2; Plumier-Clermont; Curschmann). The cases fall into three groups electrocardiographically:

1. Normal electrocardiogram, or slight changes (negative TI, II, III or deep "Q," lead I upright (16 cases): Vaquez and Donzelot, case 2; Gautier and Coeytaux; Colvin; Mandelstamm and Reinberg, cases 5, 6 and 7A; Rösler, cases 2, 3 and 4; Krestin; Gorter, case 2; Jones, cases 3 and 4; Bahn, Pol (post mortem); Fulchiero and Bruno.

2. Inversion of lead I as in complete situs inversus (10 cases): Positive (6 cases): Meyer, Mandelstamm and Reinberg, case 9; Gorter, case 5; LeWald; Rösler, case 5; Moffett and Neuhof. Probable (4 cases): Capon and Chamberlain; Rösler, Spitzer; Strothmann; Lichtman, case 1.

3. Cases difficult to classify (unusual electrocardiogram; conduction disturbance, distortion or masking) (6 cases): Biedermann; MacCallum and Resnik; Weinberger, cases 1 and 2; Mandelstamm and Reinberg, 7B; Lichtman, case 2.

Unusual Findings in Dextrocardia.—There are several instances of atypical electrocardiographic findings in dextrocardia best explained as due to the combined influence of the dextroposition and associated cardiac malformation. Such cases belong to the isolated type as well as to complete situs inversus. Cases associated with marked right ventricular hypertrophy are mainly concerned. There is no case of the inverse type of isolated dextrocardia that shows typical evidence of right ventricular predominance.

Owen:[249] Complete situs inversus with mitral stenosis and left ventricular predominance.

Abrahamson:[4] Case 2, complete situs inversus with mitral disease; electrocardiogram showed downward deflection of lead I, sinus arrhythmia and left ventricular predominance.

Clerc and Levy:[81] Case 1, complete heterotaxia; cardiac decompensation secondary to chronic emphysema and nephritis and no congenital malformation; electrocardiogram showed in lead I inverted P, upright and small R, deep S, T negative and small; lead II, P inverted, R upright and small, S deep, T upright; lead III, PRT upright.

Meyer, P.:[223] Complete heterotaxia, pulmonary stenosis and right ventricular hypertrophy; lead I, P and T negative, R slightly negative, S extremely high and positive; definite left ventricular predominance; leads II and III replace each other.

Gorter:[134] Case 4, a female, aged 7 years; clubbing of fingers, cyanosis and polycythemia; thrill; systolic murmur; lead I, P and R upright, T negative; lead II upright; lead III, P and T upright, R negative; left ventricular predominance; highest excursion in I; lead II larger than III.

TABLE 2.—*Cases of Isolated Congenital Dextrocardia Studied Electrocardiographically with Clinical and Roentgenographic Findings*

No.	Author and Date	Sex and Age	Clinical Symptoms	Roentgenogram: Aorta: Arch	Roentgenogram: Aorta: Descending	Roentgenogram: Abdominal Organs	Roentgenogram: Cardiac Shadow	Roentgenogram: Diaphragm Lower	Roentgenogram: Lung Fields	Electrocardiogram: P I	P II	P III	QRS I	QRS II	QRS III	T I	T II	T III	Comment
1	Stoerk,[328] 1911	Male 11 yr.	Dyspnea; palpitation in right side of chest	Right	Left	?	Confirms physical findings	0	0	..	..	..	..	..	..	..	..	..	"Normal electrocardiagram"
2	Moffett and Neuhoff,[229] 1915	Male 3½ yr.	Cyanosis of lips; clubbing of fingers; dyspnea; systolic thrill and murmur; septum defect; patent foramen ovale; pulmonary stenosis; patent ductus arteriosis	Left pulmonary artery not visible	Left	Stomach and colon normal (barium); liver in right hypochondriac region	Hypertrophy of right and left ventricle and right auricle; dilated left auricle	Right?	0	−	0	0	−	0	0	−	0	0	Paroxysmal auricular tachycardia with decreased auriculoventricular conduction time; large P in lead II (malformation of metacarpals)
3	Boruttau and Stadelmann,[62] 1917	?	Maternal uncle had dextrocardia; congenital cardiac malformation	?	?	?	Dextrocardia	0	0	0	0	−	0	0	−	0	0	−	"Apparently a normal curve"
4	Weinberger,[349] 1919, case 1	Male 47 yr.	Dyspnea; slight cyanosis; cardiac hypertrophy; systolic and diastolic murmurs; bradycardia	Right?	Left	Stomach and liver normal	Decompensated mirror-image heart; aorta, pulmonary artery and ventricle on right side	Right slightly	Clear	+	+	0	+	+	0	+	+	0	"Q" deep in leads I and II; (aortic insufficiency and early stenosis; cardiac decompensation; question of masked electrocardiogram by acquired cardiac lesion?)
5	Weinberger,[349] 1919, case 2	Female 21 yr.	Dyspnea; palpitation; cyanosis; systolic murmur; accentuation of second sound	0	0	0	Small portion to left of sternum	0	Right pleuropericardial adhesion	+	+	0	+	+	0	+	+	0	"Q" deep in leads I and II (heart and lungs freely movable; patent foramen ovale and ductus arteriosus?)
6	Vaquez and Donzelot,[341] 1920, case 1	Male 21 yr.	Palpitation	0	0	0	Apex forms extremity of heart (orthodiagram)	Both equal (diagram)	Clear	+	+	+	+	+	+	+	+	+	
7	Reinberg,[276] 1922 (same as Mandelstamm and Reinberg; case 5, 1928)	Male 35 yr.	No symptoms or abnormal cardiac signs	Left	Left	Liver, esophagus, stomach intestines normal (barium)	Axis above on left down to right	Right	Clear	+	+	+	+	+	+	+	+	+	(Dextrocardia noted at age of 14 years; dry left pleurisy at age of 28; liver palpable at right costal margin)
8	Meyer,[223] 1923	Female 17½ yr.	Palpitation on exertion; no abnormal cardiac signs	Right pulmonary artery on right of aorta	Right	Liver normal; stomach normal (barium)	Mirror-picture dextocardia	Right (illust.)	Clear	−	+	+	−	+	+	−	+	+	P II and T II hardly discernible; Q II pronounced; P, R, T, III more elevated than lead II; leads II and III interchanged
9	Curschmann,[88] 1924	Male 40 yr.	Systolic murmur over all ostia	0	0	0	No roentgenographic study	.....	.....	..	..	..	..	..	..	..	..	..	R I abnormally high; R II abnormally low; "normal electrocardiogram"
10	Jones,[169] 1924 case 3	Female 35 yr.	Precordial pain; dyspnea; cough	0	0	0	Dextrocardia	0	No tuberculosis	+	+	+	+	+	+	−	+	+	T I iso-electric; Q I deep; (dextrocardia known to patient for 12 years; influenza and pleurisy 2 years ago)
11	Jones,[169] 1924 case 4	Male 27 yr.	Dyspnea; presystolic thrill and bruit; diastolic murmur	0	0	0	Dextrocardia	0	Clear	+	+	+	+	+	+	−	−	+	P I partially inverted (dextrocardia recognized by army physician 7 years previously; mitral stenosis)
12	Fulchiero and Bruno,[123] 1924	Male 22 yr.	Dyspnea; palpitation; systolic murmur	Left	Left	Liver and spleen normal; stomach	Orthodiagram; normal size globular	Left (sketch)	Clear; no adhesions	+	+	+	+	+	+	+	+	+	Q I and II present; leads II and III not interchanged; no ventricular predominance (septum

12	Fulchiero and Bruno,[123] 1924	Male 22 yr.	Dyspnea; palpitation; systolic murmur	Left	Left	Liver and spleen normal; stomach normal (barium)	Orthodiagram; normal size globular heart; dextrocardia	Left (sketch)	Clear; no adhesions	+	+	+	+	+	+	+	+	Q I and II present; leads II and III not interchanged; no ventricular predominance (septum defect)
13	Gorter,[124] 1925, case 1	? 4 mo.	Cyanosis; thrill; systolic murmur	Left (wide)	Left	Liver on right	Dextrocardia	Right slightly	Clear (illust.)	+	+	+	+	+	+	—	—	—	Q I and III present; no ventricular predominance (congenital cardiac disease)
14	Gorter,[124] 1925, case 2	? 2 yr.	Systolic murmur	0	0	0	No roentgenographic study	0	0	+	+	+	+	+	+	+	+	+	Q II present; QRS I, II, III notched; right ventricular predominance (illust.) (borderline case)
15	Gorter,[124] 1925, case 4	Female 7 yr.	Cyanosis; dyspnea clubbing; thrill; systolic murmur; cardiac hypertrophy	0	0	0	Dextrocardia; apex?	Right	Clear (illust.)	+	+	+	+	+	—	—	+	+	Q I definite; R III split; left ventricular predominance (illust.) (position of apex in doubt; borderline case; congenital disease)
16	Gorter,[124] 1925, case 5	? 4 mo.	Cough; dyspnea; cyanosis; thrill; systolic murmur	0	0	Liver on right	Mirror-picture dextrocardia	Both equal	Clear (illust.)	—	+	+	—	+	+	—	+	+	Q III notched; no ventricular predominance (congenital cardiac disease)
17	Capon and Chamberlain,[69] 1925	Female 26 mo.	Fugitive systolic bruit	Not visible left lung field	?	Liver normal; stomach normal (barium sulphate)	Dextrocardia	Right (illust.)	Clear (illust.)	—	—	+	—	—	+	—	—	+	No ventricular predominance (recent left bronchopneumonia)
18	LeWald,[203] 1925	Female 24 yr.	Clinical diagnosis pleurisy	Left	Left	Abdominal organs normal (barium sulphate)	Mirror-image dextrocardia; apex to right, sharp outline	?	Clear	—	..	..	—	..	..	—	..	..	Leads II and III not given
19	MacCallum and Resnik,[211] 1926	? 10 wk.	? (Postmortem cortriloculare biatriatum)	0	0	0	No roentgenographic study	0	0	—	+	+	—	+	+	—	—	—	P I diphasic; P III split (necropsy)
20	Gautier and Coeytaux,[128] 1926	Male 18 mo.	No cardiac symptoms or abnormal signs	Right border of heart	Left	Stomach normal (air-bubble); liver normal	Axis to right of first oblique; posterior mediastinum clear	Right	Clear	+	+	..	+	+	..	+	+	..	Lead III not given
22	Colvin,[62] 1926	Female 28 yr.	Pain in left side of chest; left systolic murmur	Left	Left (illust.)	Stomach normal (barium)	Dextrocardia; apex round	Right	Clear	+	+	+	+	+	+	+	+	+	Normal electrocardiogram; lead I complexes small
23	Krestin,[184] 1927	Female 30 yr.	Dyspnea; palpitation; systolic and diastolic murmurs; irregular pulse	Right	?	Liver on right; left (barium?)	Dextrocardia; globular heart; right ventricle hypertrophy	Both equal	0	0	+	+	+	+	+	+	+	+	R I irregular; right ventricle predominance (illust.); leads II and III normal; (acquired mitral stenosis; auricular fibrillation; transposition of vessels
24	Mandelstamm and Reinberg,[213] 1928, case 6 (case 5, vide Reinberg no. 7, above)	Male 36 yr.	No symptoms or abnormal cardiac signs	Left	Left	Gastro-intestinal tract normal (barium); liver normal position	Dextrocardia; axis left above to right below and anteriorly	Right	Clear	+	+	+	+	+	+	+	+	+	Q I and II present; R III split; normal electrocardiogram (dextrocardia recognized in childhood; pneumonia and pleurisy in childhood; liver under right costal margin)
25	Mandelstamm and Reinberg,[213] 1928, case 7A	Female 7 yr.	No symptoms or abnormal signs	Right; in first and second oblique	Right; in first and second oblique	Liver and spleen normal; stomach and duodenum normal (barium)	Dextrocardia; apex on right, sharp contour	Right	Clear	+	+	+	+	+	+	+	+	+	Normal electrocardiogram (deformity of left side of chest and fissure of sternum; scoliosis included as true dextrocardia because of transposition of aorta
26	Mandelstamm and Reinberg,[213] 1928, case 7B	? 15 yr.	Dyspnea; slight palpitation in right side of chest	Left	Left	0	Dextrocardia	Right	Pleural adhesion left base	+	0	—	—	—	+	+	+	+	R I, II and II resemble left extrasystoles; R I and II notched; conduction defect?; leads II and III transposed

TABLE 2.—*Cases of Isolated Congenital Dextrocardia Studied Electrocardiographically with Clinical and Roentgenographic Findings—Continued*

No.	Author and Date	Sex and Age	Clinical Symptoms	Roentgenogram: Aorta: Arch	Aorta: Descending	Abdominal Organs	Cardiac Shadow	Diaphragm Lower	Lung Fields	Electrocardiogram: P I	P II	P III	QRS I	QRS II	QRS III	T I	T II	T III	Comment
27	Mandelstamm and Reinberg,[213] case 9	Female 14 yr.	No symptoms or abnormal signs	Right	Right?	Gastro-intestinal tract normal (barium); liver normal	Dextrocardia; smooth contours	Right	Clear	−	+	+	−	+	+	−	+	+	Leads II and III transposed (mirror-picture dextrocardia; heart and aorta)
28	Strothmann,[329] 1929	Male 9 yr.	Dyspnea and cyanosis from birth; systolic murmur; clubbing of fingers	Right; in second oblique; aorta from right ventricle	Right; in first oblique	0	Mirror-picture; right ventricle dilated; I. V. C. in left phrenicocardiac angle	Both equal	0	+	+	+	+	+	+	+	+	+	Normal electrocardiogram; paradoxical upright lead I in presence of claimed inversion (see p. 876 for explanation) (pulmonary stenosis; septal defect; aorta from right side of heart; transposition of vessels and heart)
29	Rösler,[288] 1930, case 12 (case 1, vide Rösler and Spitzer, table 1)	Male 17 yr.	Soft systolic over all ostia	Right	Right	Liver normal; stomach and duodenum normal (barium)	Pulmonary conus not visible; retrocardiac space in second oblique	Right	0	+	+	+	+	+	+	−	+	+	QRS III diphasic (mesocardia with apex to right and transposition of great vessels)
30	Rösler, case 3	Female 11 yr.	No symptoms or signs; congenital absence two fingerbreadths in father	Left	Left	Stomach normal (barium)	Apex not definite; pulmonary conus not visible; retrocardiac space in first oblique	Both equal	Clear	+	+	+	+	+	+	+	+	+	Sinus rhythm; normal electrocardiogram (multiple deformities; defects fingers both hands; syndactylism left toes; fissure lower sternum; cervical rib; dextrocardia and other anomalies considered independent)
31	Rösler, 1930, case 4	Male 33 yr.	Dyspnea on exertion; rough systolic murmur in right supraclavicular fossa	Left	Left	Liver normal; stomach normal (barium)	Dextrocardia; narrow heart; apex not definite	Right slightly	Clear	+	+	+	+	+	+	−	+	+	Q I deep; sinus rhythm (acute rheumatic fever at 15 years)
32	Rösler, 1930, case 5	Female 36 yr.	Accidental soft systolic murmur related to first sound	Right	Right	Stomach and liver normal	Mirror-image dextrocardia and vessels	Right	Clear	−	+	+	−	+	+	−	+	+	Inversion of lead I; leads II and III normal (aortic arch and portion of descending aorta in first oblique view; pulmonary artery and ascending aorta in second oblique)
33	Lichtman, 1931, case 1	Female 21 yr.	Precordial pain at age of 8 years; slight dyspnea; rough systolic murmur	Left (visualized in first oblique view)	Left	Liver normal; stomach normal (CO_2 gas)	Dextrocardia; apex round	Right	Clear	+ very low	+	+	+	+	+	− slight	−	+	Leads II and III normal; no ventricular predominance; for discussion of upright QRS I, and very low P I and inverted T I see p. 870; isolated mirror-picture dextrocardia; septal defect
34	Lichtman, 1931, case 2	Male 46 yr.	Slight dyspnea; cardiac hypertrophy; soft systolic murmur; bradycardia	Left (not definitely visualized in oblique positions)	Left	Liver normal; esophagus, stomach and duodenum normal (barium)	Dextrocardia; cardiac hypertrophy	Right	Infiltrations both bases	0	0	0	+	+	+	−	+	−	Ventricular rate 45, 55, 52; complete congenital heart block; idioventricular rhythm, simulating bundle branch block of the common type. Auricular fibrillation; normal relationship of ventricles; septal defect; retrocardiac space visualized in second

Gorter: Case 5, patient aged 4 months, dyspnea, cyanosis, systolic murmur and thrill; lead I, P and T negative, QRS, initial phase negative and positive second phase; leads II and III upright, unusually Q II and III.

Feldman: [104] Complete situs inversus with cyanosis and loud diffuse systolic murmur; lead I, P upright, R and T inverted.

Biedermann: [40] Inversion of conduction; negative QRS I and II and T I and II; atypically positive P I and II possibly due to right ventricular predominance; lead III upright.

Liotta: [203] Complete situs inversus; right ventricular predominance; lead I, P negative, QRS upright, T negative.

Mandelstamm and Reinberg: [213] Case 3, complete situs inversus; male, aged 50 years; hypertrophy of left ventricle; wide aortic arch; R and T negative in lead II.

Case 4, complete situs inversus; female, aged 24 years; congenital cardiac disease, probably pulmonary stenosis; hypertrophy of venous ventricle; cardiac decompensation; lead I, P diphasic, R initial phase negative, T diphasic; lead II larger than III; right ventricular predominance.

Abbott and Moffatt: [2] Partial heterotaxia with aplasia of left ventricle and hypertrophy of right; mirror-picture dextrocardia; leads I and II, P and T inverted, R upright, "Q" unusually deep; lead III, P diphasic, R upright, T upright; rhythm regular; normal conduction.

Strothmann: [329] Isolated complicated mirror-picture dextrocardia with pulmonary stenosis and septal defects; lead I normal and upright, left ventricular predominance.

Rösler [288] and Spitzer: [320] Right ventricular predominance; T I negative; P II and III negative; S I large.

Lichtman: Case 1, isolated mirror-picture dextrocardia with septal defect; lead I, P very low, T inverted, QRS upright; lead II, T very low.

Cases affecting the left side of the heart are rare and do not seem to exercise the same disturbing effect on the form of the electrocardiogram. This influence might be expected in cases with conus, aortic or isthmus stenosis and hearts with extremely small right ventricles (tricuspid stenosis) with left ventricular predominance in the electrocardiogram and mirror-picture dextrocardia.

Mohr: [230] Complete situs inversus with aortic stenosis; lead I typical inversion; no modification of electrocardiogram.

Weinberger: [349] Case 1, isolated dextrocardia; roentgenographic evidence of inversion but leads I and II upright, III not given; no ventricular predominance.

The first intimation of the recognition of the influence of associated malformation on the electrocardiogram was expressed by Vaquez and Donzelot (1920): "The electrocardiogram in complicated dextrocardia without inversion would be interesting in view of malformation without inversion of the cavities."

Credit for the first tangible expression of this influence is due Laubry and Pezzi (1921) who, in discussing Moffett and Neuhof's case, asserted that "mention ought to be made of those cases where the law

of the integrity of the electrical waves is found to be at fault (in the case in question the 3½ year old child had cyanosis and all signs of pulmonary stenosis and interventricular septum defect). The complex lesion itself could modify the electrical axis and give rise to a ventricular complex directed downward but would not explain the downward P. On the other hand, if the right-sided cavities were transposed, or in other words, if the venous heart were on the left, its predominant hypertrophy by reason of the lesion should have given rise to an initial ventricular complex directed upward." On this basis they would not accept this case as a definitely proved mirror-picture type.

Meyer [223] (1923) made to his knowledge an original observation in his case, of an "expression of the combined influences of situs inversus and right ventricular hypertrophy, the former by reversal of the main deflections in a peripheral direction, the latter (right ventricular hypertrophy) by a displacement of the ventricular complex in a diametral direction."

Further recognition of this influence was expressed by Feldman in his case, which he too believed to be an original observation, as the "possibility of the accompanying defect in the structure of the heart as evidenced by the bruit, determining the upright character of the P wave."

Clerc and Levy (1926), discussing the electrocardiographic findings in their case, mentioned that "hypertrophy and insufficiency of the right ventricle have by themselves brought about certain changes."

Strothmann, in a thorough study of his case, offered the following explanation of the apparently paradoxical normal upright lead I with presumed inversion of the chambers.

> The hypertrophy of the left heart is as characteristic of this heart as the inversion of the chambers as a result of the pulmonary stenosis and pulmonary defect. Its muscle is stronger. The right heart on the other hand shows definite clinical and roentgen evidence of insufficiency and dilatation. Therefore as far as the muscular divisions of the ventricles this heart is similar to a dextroposed heart without inversion of the chambers. The division of the electrical potential occurs in the normal fashion, the right-sided heart becoming negative electrically somewhat before the left (transposed hypertrophied right ventricle) whose muscle in this case being stronger offers more resistance to the conduction of the impulse from the inner to the outer surfaces thus resulting in a normal electrocardiogram.*

* The contention that while the ventricular complex may thus be affected, the P wave in Strothmann's case should remain deflected downward, is answered by him by the enlargement and dilatation of the left auricle resulting in a delay in the conduction of the excitation in this chamber, the right auricle receiving the impulse just as soon, giving a contraction expressive of relatively normal temporal relations between the two auricles.

In addition to Strothmann's case of isolated dextrocardia, discussion of the effect of associated malformation on the electrocardiogram will be found in Abbott and Moffatt's interpretation of their case of partial heterotaxia and in the comments on my cases (pp. 687 and 692).

Rösler has made casual reference to this point: "Some cases of congenital vitium (especially pulmonary stenosis and other malformations) show right ventricular preponderance. If situs inversus is present in addition (in total situs inversus), lead I shows negative P, upright QRS, and negative T waves."

There are several instances of dextrocardia with atypical electrocardiographic findings best explained as dependent on unusual degree of axis deviation of the heart. In this connection clinical and experimental observations would indicate that mere change in the position of the heart so far as the direction of its axis is concerned will not influence the negative or positive character of the electrocardiographic deflections (Lewis; Nicolai; Vaquez and Donzelot; Bordet; Samoiloff). Changes in the QRS complex of the electrocardiogram require displacement at an angle to the longitudinal axis (Einthoven, Fahr and de Waart).

Inversion of lead II as well as I has occurred in several cases of dextrocardia (Capon and Chamberlain; Moffett and Neuhof, cases 1 and 2, total situs inversus; case 8, partial heterotaxia; Willius, case 1, total situs inversus). Willius attributed this to an exaggerated inclination of the cardiac axis to the right, while Lewis attributed inversion of lead II to the bizarre deflections often found in lead III of normal subjects. In favor of the former theory are the two cases of congenital cardiac disease with enormous hypertrophy of the right side of the heart without dextrocardia in which leads I and II were inverted (Wenckebach and Winterberg, cited by Strothmann). In favor of Lewis' theory of atypical findings in lead II are Clerc and Levy's case 1 in which the inversion of P II is explained as that frequently observed normally in III, and in McLaughlin's case of combined dextrocardia and dextroversion, T II was negative and R II low, S II deep as evidence of left ventricular predominance usually noted in lead III.

Various forms of arrhythmia and disturbances in conduction have been noted to occur among the reported cases of dextrocardia and recognized by the electrocardiogram.

Abrahamson:[4] Case 2, complete situs inversus with mitral disease; lead I inverted; left ventricular predominance; sinus arrhythmia.

Case 3, complete situs inversus with systolic murmur and precordial pain; bradycardia and sino-auricular block.

Mandelstamm and Reinberg:[213] Case 7B; isolated dextrocardia without inversion; bizarre due to conduction disturbance; lead I, P upright, R resembles

left-sided extrasystole; lead II, P absent, R resembles left-sided extrasystole; lead III, P negative, R maximum height, upright, ascending limba notched; leads II and III transposed; T I, II, III upright.

Case 8, partial heterotaxia dextrocardia of inverse type; inconstant arrhythmia of sino-auricular type with atrioventricular extrasystoles; when regular, all waves deflected downward in leads I and II.

Moffett and Neuhof:[229] Isolated dextrocardia of inverse type; runs of paroxysmal auricular tachycardia lasting several or many beats with very much shortened auriculoventricular conduction time and a large auricular wave in II; evidence of auricular hypertrophy.

Krestin:[184] Auricular fibrillation; mitral stenosis.

Lichtman: Case 2, auricular fibrillation; bradycardia; complete heart block; idioventricular rhythm; ventricular complexes simulating bundle branch block of the common type.

Among the electrocardiographic abnormalities probably due to acquired disease are the cases of:

Abrahamson:[4] Case 4, total situs inversus with rheumatic pains; lead I, P not seen, R and T inverted; leads II and III, P inverted, R and T upright.

Jones:[169] Case 4, isolated dextrocardia (?) with mitral disease; P I partially inverted; T II and III negative.

Willius:[300] Case 3, total situs inversus, thyroid adenoma; left ventricular preponderance, otherwise normal.

Cases with minor "abnormal" electrocardiographic variations involving the "Q" and T waves follow. Similar changes have been obtained experimentally and in other clinical conditions in which the heart has been displaced and rotated to the right.

Weinberger: Case 1, leads I and II, deep Q.

Jones: Case 4, leads I and II, deep Q.

Gorter: Case 2, leads I and II, deep Q.

Fulchiero and Bruno: Leads I and II, deep Q.

Rösler: case 4, leads I and II, deep Q.

Mandelstamm and Reinberg: Cases 5, 6 and 7a, leads I and II, deep Q.

Gorter: Case 1, leads I, II and III, deep Q.

MacCallum and Resnik: Typical inversion of lead I, Q II unusually deep; T II and III (and I) negative.

Review of the atypical electrocardiographic findings in dextrocardia would indicate that the concomitant presence of malformation, disease or disturbances in the conduction apparatus of the heart may alter the character and direction of the main deflections. The absence of classic inversion of the first lead under such conditions does not preclude the presence of inversion of the chambers. It is claimed that under certain conditions the inversion may be entirely masked, giving a practically normal electrocardiogram (Strothmann). Interchange of leads II and III in isolated dextrocardia is a rare observation. Due allowance must be made for complicating factors in the diagnostic interpretation of the electrocardiogram in the different types of dextrocardia.

DIAGNOSIS

The problem in the diagnosis of isolated dextrocardia entails the elimination of cases of acquired dextrocardia in classic or exceptional form, the differentiation of isolated dextrocardia from complete situs inversus and determination of the presence or absence of inversion of the chambers of the heart.

Most commonly one is dealing with a dextroversion due to extrinsic causes and marked by absence of inversion of the cardiac axis. The heart is carried en masse to the right, and the apex continues to beat to the left. Exceptionally, the apex beats to the right (Chalier and Rebattu), due to a localized pleurisy. Acquired dextrocardia may cause inversion of the heart, the apex being displaced about a vertical axis (Garel and Varay). Factors usually causing dextroversion may coexist with a genuine dextrocardia (McLaughlin; Schroetter). Pleuropericardial adhesions were present in Cipriani's case of partial heterotaxia with mirror-picture dextrocardia. The concomitant transposition of other structures establishes the congenital nature of Moellenbrock's case with pleuropericardial adhesions and Breschet's case with fibrous pericarditis. The roentgenographic examination by plate and fluoroscopic screen is the most valuable aid in the demonstration of an extracardiac cause of displacement of the heart. The previous history of pleurisy and pneumonia, while strongly suggestive of an etiologic factor for the displacement, does not preclude the congenital nature of the dextrocardia (28 cases in the collected series of acceptable cases gave history or evidence of extracardiac thoracic disease).

The presence of cyanosis, cardiac murmurs and clubbing of the fingers and toes favor the congenital origin of the dextrocardia. Malformations of the heart, however, may occur in the presence of normal cardiac sounds (Aufdermauer, 10 month old child with extensive malformations; Wright and Drake, cor biloculare; Rösler and Spitzer's case; Shapiro, extensive malformations; Löwenthal, septal defect; Baumgarth, cor biloculare). Cases of complete situs inversus are also rarely complicated. The occasional association of skeletal anomalies is of doubtful significance diagnostically as to the congenital nature of the cardiac displacement. In Scheussler's case with congenital anomalies of the skeletal system, the displacement of the heart was due to an acquired pleuritis. In Mandelstamm and Reinberg's case 7A of isolated dextrocardia without inversion of the chambers, a congenital fissure of the sternum would be considered the cause of the displacement were it not for the presence of a right-sided arch and descending aorta.

The simplest method for the diagnosis of situs inversus is the demonstration of the liver in the left hypochondriac region. Palpation

of the abdominal aorta to the right of the vertebral column is weighty but not conclusive evidence of complete situs inversus. A right-sided arch and descending aorta have occurred in isolated dextrocardia without inversion of the chambers of the heart (Breschet, 1826; Mandelstamm and Reinberg, case 7a; Eschenbach) and in partial heterotaxia (Schelenz). In Sakurai's case of partial heterotaxia, the thoracic aorta ran on the right and the abdominal aorta on the left of the vertebral column. Wehn cited cases of complete situs inversus in which the descending aorta alone remained in situs solitus (Buhl; Fox). The position of the arch of the aorta is too variable to be of any diagnostic significance, save that the presence of a left aortic arch rules out complete situs inversus.

The diagnosis of the transposition of the cerebral hemispheres is aided by a history of left-handedness (Weygandt) and the diagnosis of heterotaxia of the abdominal organs by demonstration of the lower position of the right testicle. The demonstration of inversion of the lungs may be attempted by bronchography or bronchoscopy. In the absence of normal variations in the relations of the eparterial bronchus and the number of pulmonary lobes (Neumann, citing Aeby and Geipel), diagnosis of transposition of the lungs may be made. Inversion of the heart and great vessels may take place without inversion of the lungs (vide Schelenz).

The depression of the right leaf of the diaphragm occurs both in complete and in isolated dextrocardia and is of no differential value except that it rules against acquired dextrocardia.

Even in complete situs inversus, the heart must be demonstrated on the right side. Cases occur with situs solitus of the heart (Hickman, Lochte, and others. See p. 702).

Transposition of the liver and the gastro-intestinal tract is best demonstrated by the roentgenographic examination with the aid of barium sulphate or inflation with gas. Transposition of a normal gallbladder may be demonstrated by cholecystography by means of radiopaque substances.

For the diagnosis of inversion of the chambers of the heart, the electrocardiogram is the sole clinical aid. The familiar inversion of lead I is evidence of mirror-picture dextrocardia. This evidence is, however, not pathognomonic since inversion of the chambers may rarely take place in situs solitus of the heart (Alaux, citing Rokitansky, 2 cases). Inversion of leads II and III has been reported by Wenckebach and Winterberg (cited by Strothmann) in 2 cases of congenital pulmonary stenosis with enormous right-sided hypertrophy. In Shaw and Blake's case of transposition of the viscera with mirror-picture sinistrocardia, lead I was inverted. Furthermore, inversion of the

chambers may possibly occur in the absence of typical inversion of lead I (Strothmann). The electrocardiographic signs should be supplemented by roentgenographic studies. As has been pointed out, complicating disease and malformations of the heart alter the characteristic findings in both types of dextrocardia and allowance must be made for this factor in the diagnostic interpretation of the electrocardiogram. Mirror-picture dextrocardia must not be ruled out on this criterion alone.

PROGNOSIS

The average age in the cases studied by necropsy is 14 years. Most deaths occur in the first year of life. After the age of 10, the expectation of life is thirty-five years; after the age of 20 years it is forty-four years. The average age of the clinical case is 23½ years. The prognosis in the complicated case is that of congenital cardiac disease. Death commonly occurs as a result of bacterial endocarditis or tuberculosis, or it occurs suddenly.

SPECIAL LISTS OF CASES

EQUIVOCAL CASES

In the group of equivocal cases are included those which in the opinion of their authors and of other authors or in my opinion cannot finally be accepted as cases of isolated dextrocardia. When an anatomic examination has been made, the abdominal situs is not known or observations throw doubt on the congenital nature of the right-sided heart. It is to be expected that great variations will occur in this group in different reviews, depending on the interpretation, sources of information and criteria of the respective authors.

1. Moellenbrock [228] and Hoffman: [159] Pleuropulmonary and diaphragmatic adhesions present; stomach displaced to right (Aufdermauer, Foggie) suggesting a partial heterotaxia or displacement of heart, secondary to the thoracic inflammatory condition.

2. Torrez: [334] Case of ectopia cordis; pericardium missing; apex where base is usually situated; reported as doubtful by Krieger.

3. Smith, J.: [318] Description incomplete; female, aged 31 years; auricles and ventricles enlarged; superior vena cava and pulmonary veins widened.

4. Otto, [248] 1816: Case 2, question of displacement of heart due to thoracic deformity of pleurisy in adult with pulmonary tuberculosis.

5. Meckel [221] Cited as doubtful case by Krieger; case of agenesis of right lung and displacement of heart.

6. Friedberg: [119] Abdominal situs not mentioned.

7. Frickhoeffer: [118] Thoracic rib and muscle defect.

8. Allgemeinen Krankenhaus in Wien, 1857: [8] Pulmonary tuberculosis; heart not displaced far to right; probably acquired dextroversion; cited by Vehsemeyer; data incomplete.

9. Dickinson: [92] Abdominal organs not mentioned; description of heart and branches of aorta suggest complete situs inversus with malformation.

10. Boerhaave: [50] Case 1, data incomplete but possibly true case. Case 2, incomplete but probably not true case.

11. van der Hegge-Zijnen [152] (cf. de Jong [170]): Cited by Rösler as doubtful case.

12. Chabrely: [76] Mediastinitis present.

13. Niesel [241] and Sandhop: [292] Pleuritis?; no roentgenogram; clinical only; author not committed.

14. Ewart and Bennett: [102] Pneumonia present; author uncertain as to congenital nature.

15. Inches [165] Author uncertain; probably acquired.

16. Fernet: [106] Roentgenographic evidence of pleuropericardial disease.

17. Vittinghoff: [344] New-born infant; situs transversus of heart and blood vessels; brief description; thoracic deformity.

18. Paltauf; [252] Pascheles,[256] and Bamberger: [28] Congenital, but question of being secondary to pericarditis of intra-uterine origin.

19. Chapot-Prévost: [78] Surviving member of thoropagous monster; roentgenogram showed inversion of heart; abdominal organs not mentioned.

20. Alaux: [11] Deformity of chest and mitral stenosis; base displaced to right; clear space between diaphragm elevated by liver and heart; probably a dextroversion.

21. Brudzinski: [61] Cited by Rösler as a doubtful case.

22. Stone: [326] Doubtful pulmonary shadows in roentgenogram; median heart.

23. Aufdermauer: [21] Case 4, right fibrinous pleurisy drawing heart to right. Case 5, roentgenogram of right side unsatisfactory; right-sided pulmonary lesion(?).

24. Graham: [138] Cited by Rösler as doubtful case.

25. Schneider: [303] Cited by Rösler as doubtful case.

26. Fossier: [115] Cor mobile.

27. Geissler: [130] Case 6, cited by Rösler as unproved case.

28. Curti: [89] Thoracic deformity.

29. Jastrowitz: [168] Cited by Rösler as doubtful case.

30. Hesselgren: [156] Complicated by cardiac disease; cited by Rösler.

31. Clerc and Levy: [81] Case 2, eventration of the left side of diaphragm with displacement and rotation of the heart and asymmetry of chest suggest extracardia cause for displacement.

32. Lauri: [196] Four cases; incomplete data; cited by Rösler.

33. Rösler: [288] Case 6, right scoliosis; apex of heart and pulmonary artery not visualized; no electrocardiogram; question of secondary dextrocardia.

CASES INCORRECTLY REPORTED AS ISOLATED DEXTROCARDIA

The following cases are incorrectly reported in the literature as cases of isolated dextrocardias:

1. Sandifort: [293] Median heart with apex to left.

2. Wilson: [361] Median heart with apex to left.

3. Otto,[248] 1816: Case 1, unequivocally acquired dextrocardia (Becker, Schroetter).

4. Breschet: [57] Case 2, median heart with apex to left; aorta transposed down to abdomen; abdominal viscera not mentioned; may be situs inversus with situs solitus of heart.

5. Bailey: [26] Case with diaphragmatic hernia; cited by Foggie and by Moffett and Neuhof.

6. von Bamberger,[28] Pascheles [256] and Paltauf: [252] Bamberger case demonstrated by necropsy to be secondary to a pericarditis.

7. Berwald: [44] Apex pointed to left owing to localized pericardial adhesions probably the result of intra-uterine trauma (associated absence of pectoral muscle and depression of left ribs at sternum).

8. Schmid and Monnard: [301] Adhesive pleurisy responsible for cardiac displacement.

9. Duchamp: [96] Case of complete situs inversus with roentgenographic confirmation; cited by Culcer-Petresco as case of pure dextrocardia.

10. Schuessler: [306] Pleuritis causing cardiac displacement in patient with congenital anomalies of skeletal system.

11. Hoffmann, A.: [161] Roentgenogram proved tuberculosis to be cause of cardiac displacement.

12. Muller: [238] Case of arrested development with malformation of heart, liver and intestinal tract; base of heart points to right; cited by Culcer-Petresco.

13. Assmann: [19] Complete situs inversus; cited by Rösler.

CASES OF CONGENITAL DEXTROVERSION

Cases included in various reviews as cases of "dextrocardia" caused by pulmonary agenesis, rudimentary or partial agenesis, pulmonary hyperplasia, congenital cystic pulmonary disease or congenital hernia or eventration of the diaphragm are here cited. The normal axis of the heart is usually retained; rarely is it inverted in this series. There are usually displacement of the mediastinum and unequal pulmonary space on both sides.

1. Fournier: [116] Patient 30 years of age; liver on left; pulmonary agenesis.

2. Amelung: [13] Patient 31 years of age; rudimentary left lung; right, normal size with bronchiectatic cavities; fluid in left side of chest.

3. Klinz and Meckel: [180] Lung absent in right side of chest; cited by Breschet.

4. Leppington: [200] Enlargement of the left lung.

5. Cooper-Dease: [83] Patient, aged 10 months, right lung absent.

6. Maschka: [215] Pulmonary agenesis; cardiac malformation.

7. Bailey: [26] Diaphragmatic hernia.

8. Ponfick: [262] Pulmonary agenesis; cardiac malformation.

9. Klebs: [178] Pulmonary agenesis; cardiac malformation

10. Klebs and Naunyn: [179] Pulmonary agenesis; cardiac malformation.

11. Rokitansky: [286] Cystic disease of lung.

12. Barlow: [32] Pulmonary anomaly.

13. Garnier (?): [126] Abnormal breadth of left lung.

14. Wechsberg: [346] Cystic disease of lung.

15. Findlayson: [107] Pulmonary agenesis.

16. Oberwarth: [246] Infant 1 year old; hyperplastic left lung.

17. Graff: [137] Pulmonary defect.

18. Berliner: [43] Infant 2 years old; rudimentary lung; cardiac complications; roentgenogram showed right side of diaphragm much higher; intercostal spaces narrowed; postmortem examination showed agenesis of upper and middle lobes of right lung.

19. Finkelstein: [109] Pulmonary stenosis.
20. Seyffert: [312] Cystic disease of left lung.
21. Roelfs: [284] Pulmonary defect; cardiac complications.
22. Weill, Gardere, Wertheimer and Bernheim: [348] Pulmonary agenesis; cardiac complication.
23. Burghard: [63] Cystic disease of left lung.
24. de Lange: [192] Cystic disease of left lung.
25. Welsch: [350] Patient 56 years old; pulmonary agenesis.
26. Grawitz [140] and Krieger: [185] Patient 38 years old; left lung, wider; right lung, cystic.
27. Kreisch [183]
28. Kronig: [187] Wide left lung and high diaphragm on left side.
29. Carpenter,[72] 1904 and 1909: Cystic disease of left lung.
30. Potter: [266] Case 1, absent left lung; diaphragmatic hernia.
31. Carletti: [70] Female, aged 17 years; cystic degeneration of right lung; pulmonary tuberculosis cause of death.
32. Host: [164] Eventration of left leaf of diaphragm with displacement of and rotation of heart and thoracic asymmetry.
33. Berenguer: [41] Diaphragmatic hernia.
34. Benjamin: [40] Partial development of right lung; compensatory hypertrophy of left.
35. Clerc and Levy: [81] Eventration of left leaf of diaphragm with displacement of and rotation of heart and thoracic asymmetry.
36. Mandelstamm and Reinberg: [213] Cases 10 and 11, diaphragmatic hernia.
37. Ferguson: [105] Partial development of left lung and diaphragmatic hernia.

Several instances in which defects or deformity of the ribs, muscles or sternum exist in association with "Rechtslage" of the heart have been reported. The following cases are considered to be congenital cardiac displacements, secondary to the defects, and therefore not true dextrocardias. In all these instances the defects or deformity involve the left hemithorax. Cases of this type may be considered to be unequivocal cases of isolated dextrocardia when inversion of the chambers or course of the aorta coexist.

1. Frickhoeffer: [118] See list of equivocal cases.
2. Seitz: [308] Cited by Rösler.
3. Berwald: [44] Localized pericarditis; absent left pectoral muscles; depression of sternal end of left ribs; apex of heart to left.
4. Droog: [95] Pulmonary hernia.
5. Campbell: [65] Trauma with dextroversion; congenital cardiac disease (?).
6. Vittinghoff: [344] See list of equivocal cases.
7. Schlesinger,[300] Kienbock: [177] Male, aged 22 years; roentgenographic evidence of aorta to left, diaphragms at equal level; defect of rib and muscle on left side; pulmonary hernia.
8. Silberstein: [316] Case 1, male, aged 9 years; aorta to left; diaphragms equal; defect of left rib; syndactylism of left hand.

Case 2, female, aged 5 months; roentgenographic evidence of congenital scoliosis; high position of right shoulder; seven rudimentary ribs on left side; defect in left mamma and intercostal muscles.

9. Rieder: [279] Cases 1 and 2.

10. Cade, Rebattu and Gras:[64] Male, aged 29; roentgenographic evidence, axis of heart from above down, right to left; electrocardiogram normal; deformity; flattening of left side of chest; congenital displacement related to cause of thoracic deformity.

11. Schuessler:[306] Acquired dextroversion in a female of 11 years due to pleuritis in a patient with supernumerary ribs and vertebra and scoliosis.

12. Laubry and Esmein:[194] Male, aged 29 years; abdominal viscera normal; no inversion of lead I; congenital deformity of left hemithorax; atrophy of left breast.

13. Vaquez and Donzelot:[341] Case 1, male, aged 20; no pleural adhesions; lead I upright; congenital sternal depression and atrophy of left hemithorax.

14. Winokurow:[364] Female, aged 8 years; aorta to left in roentgenogram; upright waves, leads not given in electrocardiogram; thoracic deformity; pectoral defect.

15. Karplus:[174] Multiple malformations in infant; right lateral abdominal hernia; aberrant kidneys; anomaly of end of sternum (tip of xiphoid pointed forward); malformation of heart.

16. Melzner:[222] Case 2, male, aged 19 years; left of face smaller; high scapula; pectoral defect.

17. Wigger:[358] Cited by Rösler.

18. Dietlen:[93] Male, aged 13 years; roentgenogram; lead I of elecrocardiogram not inverted; congenital malformation of heart; absent ensiform cartilage; abdominal heart (diverticulum of heart).

19. Reuss:[278] Congenital scoliosis; causing dextroversion.

SITUS INVERSUS OF VISCERA WITH SITUS SOLITUS OF THE HEART

In antithesis to isolated dextrocardia are those rare cases of situs solitus occurring in situs inversus viscerum. The sinistrocardia may likewise be of the mirror-picture type or with normal relation of its chambers. In Shaw and Blake's case of this series, inversion of the first lead of the electrocardiogram was noted. The collected cases follow:

1. Gruber:[143] Cited by Wehn.

2. Hickman:[157] Male infant, aged 6 weeks; cyanosis; normal relation of ventricles; auricles and aorta transposed; patent foramen ovale; ventricular septum defect; absence of pulmonary artery; pulmonary veins enter right auricle; lungs transposed.

3. Lochte:[207] Ventricles not transposed; auricle transposed; aorta and pulmonary artery from right ventricle; ventricular septum defect.

4. Griffith:[142] Clinical and postmortem evidence; male, aged 9 months; cyanosis; systolic murmur; lungs transposed; great vessels transposed; hypoplastic pulmonary conus; hypertrophy both ventricles; pulmonary stenosis; ventricular septum defect; patent ductus arteriosus; auricles transposed; ventricles normal relation.

5. McCrae:[218] Gallbladder also not transposed; male infant, aged 49 days; transposition of auricles and ventricles, hypertrophied right ventricle (four fifths of bulk); absent pulmonary artery; aorta from right ventricle.

6. Muller-Herman: Personal recollection of Aufdermauer of case in which the chambers were inverted.

7. Royer and Wilson: [289] Clinical and postmortem evidence; male, aged 6½ years; cyanosis; systolic murmur and thrill; right testicle lower than left; lungs transposed; rudimentary left ventricle; ventricles normal relationship; auricles transposed; aorta and pulmonary artery from right ventricle; tricuspid valve on right side of heart; mitral and pulmonary stenosis; septal defect; patent foramen ovale.

8. Shaw and Blake: [313] Male, aged 2 years; clinical evidence only; pneumonia; systolic murmur; roentgenographic and electrocardiographic examination; transposition of abdominal organs; mirror-picture sinistrocardia (inversion of lead I and right axis deviation).

9. Miller: [227] Clinical and postmortem evidence; a female infant, 10 weeks old; cyanosis; bronchopneumonia; transposition of aorta; pulmonary artery and aorta from left ventricle; hypertrophy of left ventricle and right atrium; absent inferior vena cava; septal defects; persistent ductus arteriosus; abdominal organs transposed; lungs not mentioned.

SUMMARY

Isolated dextrocardia is defined in its strictest sense as a primary independent dextroposition of the heart.

Two personal cases are presented with unusual electrocardiographic findings, the result of associated congenital cardiac malformations and their effects.

Etiologic, pathogenic and anatomic considerations are reviewed.

A comprehensive classification inclusive of known and possible anatomic variations is presented.

A clinical analysis of the symptoms, signs, roentgenographic and electrocardiographic evidence and diagnostic features is attempted, based on a study of 161 cases of isolated dextrocardia reported in the literature.

A group of equivocal cases, concerning which there is some doubt as to admission under the category of isolated dextrocardia as here defined, is recorded.

A group of cases incorrectly reported as isolated dextrocardia is listed.

Cases of congenital dextroversion cited in the literature as cases of isolated dextrocardia have been compiled.

BIBLIOGRAPHY

Unless otherwise indicated, the original text was consulted. The outstanding bibliographies are found in the uncritical reviews of Moffett and Neuhof (M. & N.),[229] the thesis of Culcer-Petresco (C-P.),[86] the more definitive reviews of Foggie [114] and Clerc and Bobrie (C. & B.),[80] the excellent clinical study of Mandelstamm and Reinberg (M. & R.) [213] and the most thorough anatomic, electrocardiographic and roentgenologic analysis of Rösler.[288] In the citations the abbreviations are referred to.

1. Abbott, M. E., in Osler: Modern Medicine, Philadelphia, J. B. Lippincott Company, 1927, vol. 4, pp. 660-664; in Blumer: Bedside Diagnosis, Philadelphia, W. B. Saunders Company, 1928, vol. 2, pp. 360-362.

2. —— and Moffatt, W.: Mirror-Picture Dextrocardia Complicated by Mitral Aplasia and Pulmonary Hypoplasia, with Great Hypertrophy of the Transposed "Right" Chambers, Canad. M. A. J. **20**:611, 1929.

3. Abernethy, J.: Uncommon Transposition of the Heart and Distribution of the Blood Vessels; Together with Very Strange Singular Formation of the Liver, Phil. Tr. Roy. Soc. London, 1793, pp. 58-63; cited by Foggie, C. & B., M. & N., M. & R., Lochte, Aufdermauer; abstr. in Krieger's thesis.

4. Abrahamson, L.: Four Cases of Congenital Dextrocardia Including a Case with Sino-Auricular Block, Quart. J. Med. **18**:335, 1924-1925.

5. Accolas, A.: Transposition du coeur à droite, J. de méd. et de chir. prat. **46**:258, 1875.

6. Ackerman, cited by Herxheimer, in Schwalbe, E.: Die Morphologie der Missbildung des Menschen und der Tiere, Jena, Gustav Fischer, 1910, pt. 3, p. 436; cited by Laubry and Pezzi.

7. Adie: Case of Misplacement of Heart, Indian M. Gaz. **25**:117, 1890; cited by M. & N.

8. Aerztl. Ber. d. k. k. allg. Krankenh. zu Wien, 1857, p. 97; cited by Vehsemeyer, M. & N.; abstr. in Becker's thesis (original not accessible).

9. Aimé, P.: Inversion viscérale abdominale sans inversion thoracique, Arch. d. mal. de l'app. d. digestif **17**:557, 1927; cited by Rösler.

10. Aitken, R.: A Case of Congenital Transposition of the Heart, Brit. M. J. **2**:428, 1917; abstr. in Duval's thesis.

11. Alaux, L.: Contribution a l'étude clinique et anatomo-pathologique de la dextrocardie sans heterotaxie, Thèse de Lyons, 1902; cited by M. & N., C. & B.

12. Alvarenga, P. F. da Costa: Rémarques sur les dextrocardies à propos d'un cas non encore décrit: La trochocardie, J. de méd., chir. et de pharmacol. **47-48**:1758, 1869.

13. Amelung: Das Herz auf der rechten Seite und gänzliches Fehlen des linken Lungenflügels, J. d. pract. Heilk. **43**:15, 1816; cited by Rösler.

14. Anderson, L. A. P.: A Note on a Case of Dextrocardia in a Mouse, Indian J. M. Research **10**:1117, 1922-1923.

15. Angyán, B.: Dextrocardia cum insufficientia valvulae bicuspidalis, Orvosi hetil. **43**:561, 1899; cited by Rösler (original not accessible).

16. Anselmi, E.: Sopra un caso di trasposizione del cuore a destra, Riv. veneta di sc. med. **8**:555, 1888; cited by C-P.

17. Arnaud, H.: Présentation d'un cas d'anomalie de position du coeur, Compt. rend. Soc. de biol. **3**:4, 1891; cited by M. & N.

18. Arrese, D. G., and Alvarez, A. C.: Dos casos de dextrocardia congenita; uno con transposicion visceral y otro sin ella, Arch. d. med., cir. y espec. **28**:149, 1928; cited by Rösler.

19. Assmann, H.: Die klinische Röntgendiagnostik der inneren Erkrankungen, Leipzig, F. C. W. Vogel, 1928, vol. 1, p. 104.

20. Auche, B., and Boyer, B.: Dextrocardie pure sans inversion générale, J. de méd. de Bordeaux **27**:413, 1897; cited by M. & N.; abstr. by C-P.

21. Aufdermauer, E.: Ueber Dextrocardia congenita et acquisita, Inaug. Diss., Zurich, 1907; cited by Foggie, M. & N.; abstr. by C-P.

22. Augey: Dextrocardia congénitale sans inversion viscerale, Thèse de Toulouse, 1924-1925; cited by M. & R.

23. Aylward, R. D.: Congenital Heart Block, Brit. M. J. **1**:943, 1928.

24. von Baer, C. E.: Ueber Entwicklungsgeschichte der Tiere, Konigsberg, Borntträger, 1828; cited by Laubry and Pezzi.

25. Bahn, K.: Ueber isolierte Dextrocardie mit Isthmusstenose der Aorta und Endocarditis lenta, Deutsches Arch. f. klin. Med. **146**:297, 1925; cited by M. & R., Rösler.

26. Bailey, H. W.: A Case of Transposition of the Greater Part of the Abdominal Viscera into the Left Cavity of the Thorax, Tr. Obst. Soc. **10**:6, 1869; cited by Foggie, M. & N.

27. Ballentyne: Manual of Antenatal Pathology and Hygiene, Edinburgh, W. Green & Company, 1906; cited by Doolittle.

28. von Bamberger, H.: Dextrocardie ohne Situs viscerum innerus, Wien. med. Bl. **11**:205, 1888; Deutsche med. Wchnschr., 1888, no. 11; K. K. Gesellsch. der Aertzte; cited by Foggie, C. & B., Abbott; abstr. in Becker and Alaux's theses.

29. Bard, L.: Refoulement du coeur à droite et dextrocardie congénitale, Lyon méd. **71**:583, 1892; **72**:15, 1893; cited by Foggie, C.-P., C. & B., M. & N., Meyer.

30. Du refoulement du coeur à droite par les épanchements pleuraux, Med. mod. **8**:185, 1897.

31. Barié, E.: Sur un cas de cyanose (maladie bleue) chez un malade atteint d'inversion viscérale, Bull. et mém. Soc. méd. d. hôp. de Paris **11**:486, 1894; cited by Caubet and Baylac.

32. Barlow: Atelectasis of Lungs with Emphysematous Cyst, Med. Times & Gaz. **1**:22, 1880; cited by Rösler.

33. Baumann: Acht Fälle von Situs inversus viscerum totalis, Inaug. Diss., Zurich, 1917; cited by Rösler.

34. Baumgarth, H.: Cor biloculare mit Dexiokardie, Inaug. Diss., Halle, 1902; cited by Nagel, Foggie, M. & N., M. & R.

35. Bayer: Arch. gén. de méd. **23**:90, 1850; Gaz. méd. de Paris, vol. 20, series 3.

36. de Bary: Virchows Arch. f. path. Anat., 1864, p. 430; cited by Wehn.

37. de Beauvais, cited by Falck.

38. Becker, E.: Ueber Dexiocardie, Inaug. Diss., Jena, 1891; cited by Foggie, Nagel, M. & N., Vehsemeyer.

39. Benfey, A.: Beiträge zur Lehre von den angeborenen Herzkrankheiten, Inaug. Diss., Berlin, 1903; cited by M. & N.

40. Benjamin: Case Presentation, Verhandl. d. München. Gesellsch. f. Kinderh., 1912; Jahrb. f. Kinderh. **75**:367, 1912; cited by M. & N.

41. Berenguer: Semana méd. **19**:549, 1912; cited by M. & N.

42. Berks, A. R.: Ein interessanter Fall von angeborener Anomalie des Herzens, Wien. klin. Rundschau **10**:497, 1896; cited by Foggie, M. & N.

43. Berliner, M.: Ein Fall von Agenesie des Oberund Mittellappens des rechten Lunge mit Dextroversio cordis, Beibl. z. d. Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **8**:70, 1909; cited by Rösler.

44. Berwald: Ein Fall von Dextrocardia, Berl. klin. Wchnschr. **29**:1022, 1892; cited by Foggie, M. & N.

45. Bianchi: Pediatria **36**:1221, 1928; cited by Rösler.

46. Biedermann, H.: Med. Klin. **22**:1115, 1926; Gyógyászat, 1926, vol. 66, no. 23; Personal communication to Rösler.

47. Bienfait: Situation du coeur à droite, Bull. Soc. méd. de Reims, 1873, pp. 76-78; original not accessible; cited by M. & N.

48. Birmingham, A.: Extreme Anomaly of the Heart and Great Vessels, J. Anat. & Physiol. **27**:139, 1892-1893.

49. Blumenfeldt, E.: Die angeborenen Herz- und Gefässkrankheiten, in Kraus, F., and Brugsch, T.: Spezielle Pathologie und Therapie, Berlin, Urban & Schwarzenberg, 1925, vol. 1, pt. 4; cited by M. & R.

50. Boerhaave, cited by Krieger.

51. Bonheim, P.: Ueber Dextrocardia, Inaug. Diss., Kiel, 1900.

52. Boruttau and Stadelmann: Leitfaden der klinischen Electrokardiographie, 1917, p. 21; cited by Rösler.

53. Botteri, J. H.: Ein Fall von "Dextroversio cordis," Wien. klin. Wchnschr. **27**:325, 1914.

54. Bouillaud, J.-B.: Traité clinique des maladies du coeur, Brussels, H. Dumont, 1835, vol. 2, p. 546; cited by Krieger.

55. Bramwell, B.: Congenital Misplacement of the Heart in Which the Organ Is Situated on the Right Side of the Body in Which the Liver Remains in Its Normal Position, Tr. Med.-Chir. Soc. Edinburgh **1**:33, 1881-1882; cited by Foggie, M. & N.

56. —— Atlas of Clinical Medicine, Edinburgh, 1896, vol. 3, p. 116; cited by Foggie, M. & N.

57. Breschet, G.: Mémoire sur l'ectopie de l'appareil de la circulation et particulierement sur celle du coeur, Répert. gén. d'anat. et de physiol. path. **2**:1, 1826; cited by Foggie, M. & N., Schroetter; abstr. in Alaux and Krieger's theses.

58. —— Bull. Soc. anat. de Paris, 1841, p. 39; cited by Wehn.

59. Broman: Normale und abnormale Entwicklung des Menschen, Wiesbaden, J. F. Bergmann, 1911; cited by Rösler.

60. Brooks, N. P.: A Case of Transposition of the Heart, Med. Rec. **79**:962, 1911; cited by M. & N.

61. Brudzinski, J.: Dextrocardie congénitale sans inversion des autres viscères chez un enfant, Gaz. lek. **22**:639, 1902; cited by M. & N.

62. von Buhl, L.: Transposition sämmtlicher Eingeweide, Stenose des Conus arteriosus pulmonalis, Defekt des Septum ventriculorum, Verlauf der Aorta links an der Wirbelsäule, Mitt. a. d. path. Inst. z. München, 1878, pp. 311-324; cited by Wehn.

63. Burghard, E.: Hochgradige Verlagerung des Mediastinums beim Säugling infolge kongenitaler Bronchiektasie im linken Oberlappen, Fortschr. a. d. Geb. d. Röntgenstrahlen **34**:308, 1926; cited by Rösler.

64. Cade, A.; Rebattu, J., and Gras, R.: Les difficulties de classification nosologique des dextrocardies, Province méd. **24**:206, 1913; cited by M. & N.

65. Campbell, G. G.: Cardia-dextra, Montreal M. J. **24**:515, 1895-1896; cited by Rösler.

66. Campergue, B.: Contribution à l'étude de la cyanose congénitale, Thèse de Paris, 1912-1913.

67. Capitan, L.: Un cas d'inversion du coeur exclusivement, Compt. rend. Soc. de biol. **5**:1104, 1898.

68. de Capite, A.: Two Cases of Situs Viscerum Inversus with Congenital Heart Disease, Pediatria **32**:1175 (Oct. 1) 1924.

69. Capon, N. B., and Chamberlain, N.: A Case of True Dextrocardia, Lancet **1**:918, 1925; cited by M. & R.

70. Carletti, M.: Un caso di destrocardia congenita du causa rara, Gazz. d. osp. **27**:1354, 1906.

71. Carmichael, J.: Congenital Heart Disease, Patent Ductus Arteriosus, Mitral Stenosis, Edinburgh Hosp. Rep. **2**:298, 1894; Tr. Med.-Chir. Soc. Edinburgh **12**: 237, 1893; cited by M. & N., Rösler.

72. Carpenter, G.: Curious Congenital Cysts of the Lung Associated with Dextrocardia Caused by Pressure from the Cystic Lung, Brit. J. Child. Dis. **1**:160, 1904; cited by M. & N.

73. Carter, E. P., and Howland, J.: A Note upon the Occurrence of Congenital Atrio-Ventricular Dissociation: Report of a Case of Congenital Complete Heart Block, Bull. Johns Hopkins Hosp. **31**:351, 1920.

74. Caubet and Baylac: Cyanose congénitale et inversion viscérale complète, Arch. méd. de Toulouse **2**:329, 1896; abstr. by C-P.

75. Cautley, E.: Discussion of Whipham's Case, Proc. Roy. Soc. **2**:169, 1909.

76. Chabrely: J. de méd. de Bordeaux **18**:16, 1888-1889.

77. Chapman, H. G.: A Case of Dextrocardia, Intercolon. M. J. Australas. **5**:309, 1900.

78. Chapot-Prévost: De l'inversion du coeur chez un des sujets composants d'un monstre double autositaire vivant, de la famille des pages, Compt. rend. Acad. d. sc. **132**:223, 1901; cited by M. & N.

79. Cipriani, C.: Cuore unicavitario; trasposizione polomonale; polisplenia in soggetto destrocardico morto a 20 anni, Sperimentale **66**:127, 1890; cited by Foggie, C. & B., M. & N.; abstr. in Alaux's thesis.

80. Clerc, A., and Bobrie, J.: Réflexions sur un cas de dextrocardie pure, Arch. d. mal. du coeur **11**:145, 1918; À propos de la dextrocardie pure, ibid. **11**: 277, 1918; Soc. méd. des Hôp., 1917, no. 8, p. 436.

81. —— and Levy, R.: Réflexions sur deux cas de dextrocardie, Bull. et mém. Soc. d. hôp. de Paris **50**:63, 1926.

82. Colvin, L. T.: Report of a Case Showing an Unusual Type of Dextrocardia, J. Michigan M. Soc. **25**:12, 1926.

83. Cooper, G.: A Case of Malformation of the Thoracic Viscera: Imperfect Development of Right Lung and Transposition of Heart, London M. Gaz. **18**:600, 1836; cited by Gruber, Foggie, M. & N.

84. Corsdress, O.: Bilocular Heart with Situs Inversus, Monatschr. f. Kinderh. **28**:193, 1924.

85. Crispino, M.: Un caso di destrocardia congenita pura, Riforma med. **16**: 436; 447; 459, 1900; cited by Foggie; Moffett and Neuhof.

86. Culcer-Petresco, M.: Quelques considérations à propos d'un cas nouveau de dextrocardie congénitale, Thèse de Paris, 1912; cited by M. & N., C. & B.

87. Curschmann, H.: Anat. Hefte **57**:405, 1919; cited by Bahn.

88. —— Angeborene Dextrokardie ohne Situs inversus, München. med. Wchnschr. **71**:1002, 1924; cited by Rösler.

89. Curti, E.: A proposito di un caso di destrocardia, Gazz. internat. di med. **16**:947, 1913; cited by M. & N., Rösler; original not accessible.

90. Dalton, N.: Dextrocardia; Left Superior Vena Cava; Endocarditis, Tr. Path. Soc. London **50**:41, 1898-1899.

91. Darnall, W. E.: Congenital Dextrocardia, Med. News **80**:446, 1902; cited by M. & N.

92. Dickinson: Tr. Path. Soc. London **17**:83, 1866.

93. Dietlen, H.: Herz und Gefässe im Röntgenbild, Leipzig, J. A. Barth, 1923, p. 226.

94. Doolittle, W. F.: Congenital Dextrocardia, Boston M. & S. J. **157**:662, 1907; cited by M. & N., M. & R.

95. Droog, E. A. M.: Een geval van congenitale dexterocardia met herni pulmonalis, Nederl. tijdschr. v. geneesk. **30**:872, 1894; cited by Löwenthal, M. & N.

96. Duchamp: Un cas de dextrocardie avec inversion viscérale, générale; application des rayons X, Loire méd. **17**:87, 1898; abstr. in C-P.'s thesis.

97. Duval, P.: Contribution à l'étude des dextrocardies, Thèse de Paris, 1919.

98. Eguchi, K.: Situs Viscerum Inversus and High Grade Anomalies of Circulation System, Nihon Byorigakukei, Sashi, no. 13; cited by Sakurai.

99. Einthoven, P. H.: Het electrocardiogram bij aangeboren hartgebreken, Nederl. tijdschr. v. geneesk. **2**:1944, 1914.

100. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275, 1913.

101. Eschenbach, C. E.: Obs. anat. chir-med. rariosa, 1769, pp. 1-5; cited by Vehsemeyer, Löwenthal, M. & N.; abstr. in Krieger's thesis.

102. Ewart, W., and Bennett, W. H.: Case of Dextrocardia, Tr. M. Soc. London **14**:438, 1891; cited by Foggie, M. & N.

103. Falck, P.: Ein Fall von congenitaler Dextrocardia nach klinischen und graphischen Untersuchungen, Greifswald University Thesis, 1877; cited by M. & N., Rösler; vide Mosler,[236] same case.

104. Feldman, W. M.: A Case of Transposition of Viscera with a Peculiar Electrocardiogram in an Infant Three Weeks Old, Brit. J. Child. Dis. **22**:136, 1925.

105. Ferguson, V. L.: Dextrocardia and Other Abnormalities, Brit. M. J. **2**:894, 1928.

106. Fernet: Un cas d'ectopie cardiaque (dextrocardie) sans inversion des viscères; interprétation pathogénique, Bull. et mém. Soc. méd. d. hôp de Paris **13**:873; 885, 1896; cited by M. & N.

107. Findlayson: Proc. Anat. Soc. Great Britain & Ireland, 1901, p. 38; cited by Rösler; original not accessible.

108. Fingerhuth: Zwei Fälle von Transposition der grossen Herzarterienstamme, Zurich, 1901; cited by Geipel, 1902.

109. Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, 1912, vol. 2, p. 60; cited by Rösler.

110. Fischer, B.: Situs inversus totalis bei einem 21 jährigen Manne mit schweren kongenitalen Herzfehler.

111. Flatau, G.: Case Presentation, Verhandl. d. Berl. Gesellsch. f. Psychiat. u. Nervenkrankh., Neurol. Centralbl. **22**:643, 1903.

112. Fleming, G. B., and Stevenson, M. M.: Heart Block Associated with Congenital Malformation of Heart, Arch. Dis. Childhood **3**:221, 1928.

113. Fodl: Pest. med.-chir. Presse **45**:497, 1909; abstr. in C-P.'s thesis.

114. Foggie, W. E.: Dextrocardia, Cor Triloculare Biventriculare, Edinburgh M. J. **5**:428, 1910; cited by Jones, M. & R.

115. Fossier, A. E.: Displacement of the Heart: Report of Cases, New Orleans M. & S. J. **63**:342, 1910-1911; cited by M. & N., Rösler.

116. Fournier: Dictionnaire des sciences médicales, 1813, vol. 4, p. 150; cited by Rösler; original not accessible.

117. Fox: London M. & Phys. J., 1824; cited by Wehn; original not accessible.

118. Frickhoeffer: Beschreibund einer Difformität des Thorax mit Defect der Rippen, nebst Bemerkungen über die Herzbewegung, Virchows Arch. f. path. Anat. **10**:474, 1856; cited by Rösler.

119. Friedberg, H.: Die angeborenen Krankheiten des Herzens und der grossen Gefässe des Menschen, Leipzig, W. Engelmann, 1844; cited by Rösler.

120. Fröhlich, T.: Situs transversus bei drei Geschwistern. Appendicitis (Operation), München. med. Wchnschr. **69**:1384, 1922; cited by Mull, M. & R., Rösler.

121. Frommer, I.: Seltene Fälle in der Privatpraxis, Fall von Dextrocardie, Pest. med.-chir. Presse **36**:985, 1900; cited by Rösler.

122. Fukuski: Un cas de situs inversus avec rétrécissement pulmonaire, Med. Gesellsch., 1908; cited by Meyer.

123. Fulchiero, A., and Bruno, G.: Le destrocardie pure, Minerva med. **4**:869, 1924.

124. Fumaioli, G.: Morbo ceruleo, destrocardia, cardiopatia congenita, Gazz. d. osp. **43**:509, 1922; cited by Rösler.

125. Gamage: Hornsche Arch., 1818; cited by Wehn.

126. Garnier, C.: Un cas de dextrocardie avec autopsie, Presse méd. **2**:15, 1899; cited by Rösler.

127. Garvin, J. A.: Dextrocardia with Pulmonary Artery Arising from the Aorta: Case Presentation, Am. J. Dis. Child. **34**:133 (July) 1927; cited by Rösler.

128. Gautier, P., and Coeytaux: Dextrocardie congénitale pure et isolée, Rev. franç. de pediat. **2**:355, 1926; cited by M. & R. and Rösler.

129. Geipel, P.: Weitere Beiträge zum Situs transversus und zur Lehre den Transpositionen der grossen Gefässe des Herzens, Arch. f. Kinderh. **35**:112, 1903; abstr. C-P., Wilson and Royer, Schelenz (vide 1899 case).

130. Geissler: Ueber Dextrokardie, Wien. klin. Rundschau **25**:564; 584, 1911; cited by M. & N., Rösler.

131. Geoffroy-St.-Hilaire: Historie générale et particulière des anomalies de l'organisation chez l'homme et les animaux, Paris, J. B. Ballière, 1832; cited by M. & N., Falck.

132. Gerrard, P. N.: A Case of Dextrocardia, Lancet **1**:1060, 1896; cited by Löwenthal; Foggie; Moffett and Neuhof; Clerc and Bobrie.

133. Giovannini, E.: Di un caso tipico di destrocardia, Policlinico **20**:1479, 1913; cited by M. & N., C. & B.; abstr. by Duval.

134. Gorter, E.: Sur la dextrocardia, Acta pediat. **4**:125, 1925; cited by M. & R., Rösler.

135. Gossage: Tr. Clin. Soc. London **34**:220, 1901; cited by C-P., Foggie, M. & N.

136. Graanboom: Ein Fall von Dextrocardie mit Transposition von allen grossen Gefässen, Ztschr. f. klin. Med. **18**:185, 1891; cited by Foggie, Nagel, C. & B., M. & R.

137. Graff, E. V.: Angeborene Hyperplasie der einen Lunge bei gleichzeitiger Bildung der anderen, München. med. Wchnschr. **52**:598, 1905; cited by Rösler.

138. Graham, J. H. P.: Clinical Note on a Case of Complete Dextrocardia, J. Roy. Army M. Corps **7**:498, 1906; cited by M. & N., Rösler.

139. Grau, H.: Ueber den Einfluss der Herzlage auf die Form des Elektrocardiogramms, Ztschr. f. klin. Med., 1910, vol. 69, nos. 3 and 4; cited by Neumann.

140. Grawitz, P.: Ueber angeborene Bronchiectasie, Virchows Arch. f. path. Anat. **82**:217, 1880; cited by Rösler.

141. Griffith, J. P. Crozier: A Case of Transposition of the Viscera and the Great Vessels, with Pulmonary Stenosis and Perforate Septum Ventriculorum, Univ. M. Gaz. **7**:666, 1899.

142. Griffith, Wardrop: Transposition of Heart, Brit. M. J. **1**:1287, 1897; cited by Foggie, M. & N.

143. Gruber, W.: Ueber das Vorkommen eines Mesenterium commune für das Jejuno-Ileum und die grössere Anfangshälfte des Dickdarms bei seitlichen Transposition der Viscera aller Rumpfhhlen, Arch. f. Anat. u. Physiol., 1865, p. 558.

144. Gruber, G. B., and Reisinger, M.: Situs Inversus und Communicatio rectourethralis, bei Mastdarmatresie, Ztschr. f. urol. Chir. **13**:73, 1923; Zentralbl. f. Chir., 1924, p. 1093; cited by Mull.

145. Grünfeld, E.: Ein Fall von Dextrocardie, Prag. med. Wchnschr. **14**:2, 1889; cited by Foggie, C-P., M. & N.

146. Grunmach, E.: Ueber angeborene Dexiocardie verbunden mit pulmonal Stenose und Septumdefekten des Herzens ohne Situs viscerum inversus, Berl. klin. Wchnschr. **27**:22, 1890; cited by Foggie, M. & R., Lochte; abstr. in Alaux's thesis.

147. Gruss, A.: Ein Fall von Dextrocardie ohne Situs perversus der übrigen Brust und der Bauchorgane, Wien. med. Bl. **11**:129; 202, 1888; cited by Foggie, M. & N.; abstr. by C.-P., Becker.

148. Gutwasser, C.: Ueber einen Fall von Cortriloculare-biatriatum, Inaug. Diss., Göttingen, 1870; cited by Schwalbe, Herxheimer.

149. Hammer, G.: Situs inversus aortae (hohe Rechtslage der Aorta), Fortschr. a. d. Geb. d. Röntgenstrahlen **34**:517, 1926.

150. Hawkins, F. H.: A Case of Displacement of the Heart to the Right Side, the Other Viscera Being Normal in Position; Pulmonary Stenosis, with Regurgitation, Tr. Clin. Soc. London **24**:250, 1891; cited by Foggie, M. & N., Rösler.

151. Hawthorne, C. O.: Case Presentation, Society for Study of Disease of Children, Brit. M. J. **1**:1186, 1907; cited by Foggie, M. & N., Rösler.

152. van der Hegge-Zijnen, B. G.: Een geval van dextrocardie, Nederl. tijdschr. v. geneesk. **1**:432, 1871; cited by Rösler.

153. Heimann: Ueber eine Anomalie der Lage des Herzens, Berl. klin. Wchnschr. **29**:188, 1892; cited by Foggie, M. & N.

154. Henoch: Ref. Krieger; cited by Foggie; abstr. by Krieger.

155. Herxheimer, G.: Missbildungen des Herzens und der grossen Gefässe, in Schwalbe: Die Morphologie der Missbildungen des Menschen und der Tiere, Jena, Gustav Fischer, 1910, vol. 3, p. 436; cited by Laubry and Pezzi.

156. Hesselgren: Ett fall av kongenitalt hjärtfel med abnormt rörligt hjärta, Hygiea **81**:642, 1919; cited by Rösler.

157. Hickman: Tr. Path. Soc. London **20**:88, 1869; cited by Laubry and Pezzi, Abbott.

158. Hochsinger: Case Report, Gesellsch. f. inn. Med. u. Kinderh. in Wien., (Pediat. Sect.) Deutsche med. Wchnschr. **2**:1607, 1906.

159. Hoffman, F.: Cardianstrophe admiranda seu cordis inversio, 1671; cited by Breschet, M. & N.

160. Hofmann, A. H.: Familiärer Situs inversus, Zentralbl. f. Chir. **53**:1633, 1926; cited by M. & R., Rösler.

161. Hoffmann, A.: Cor.-Bl. f. schweiz. Aerzte, 1905, vol. 38.

162. Hoke: Ueber das EKG eines Falles von Situs viscerum inversus totalis, München. med. Wchnschr. **58**:802, 1911.

163. Holt, L. E.: Congenital Malformation of the Heart Resembling Dextrocardia; Entire Absence of the Septum Ventriculorum; Pulmonary Stenosis and Patent Foramen Ovale, Arch. Pediat. **7**:81, 1890.

164. Host, H. F.: Dextrokardi, Norsk mag. f. lægevidensk. **9**:735, 1911; cited by M. & N.

165. Inches, P. R.: A Case of Dexiocardia, Maritime M. News **3**:63, 1891; cited by M. & N.

166. Indemans, J. W. M.: Dextrocardia congenita or situs cordis inversus, Nederl. tijdschr. f. geneesk. **62**:1405, 1918; cited by Rösler.

167. Jasinski: Ein Fall von angeborener Herzlage in der rechten Brusthälfte, Wien. Med.-Halle **2**:323, 1861; cited by M. & N.

168. Jastrowitz: Dextropositio cordis bei Kyphokoliose mit Differenz des Pulses im beiden Armarterien, München. med. Wchnschr. **56**:793, 1919; cited by Rösler.

169. Jones, H. W.: Types of Dextrocardia, Brit. M. J. **1**:147, 1924.

170. de Jong: Inaug. Diss., Leyden, 1871; cited by Rösler; original not accessible.

171. Josué, O.: Rétrécissement congénital de l'artère pulmonaire avec communication interventriculaire, allodromie par destruction de la branche terminale gauche du faisceau de His, Bull. et mém. Soc. d. hôp. de Paris **43**:408, 1919; cited by Meyer.

172. Joukovsky: Malformation congénital du couer chez les enfants, Petersburg, 1913; Arch. d. mal. du coeur **7**:287, 1914; cited by Rösler.

173. Kalisher, S.: Ueber angeborene Muskeldefect, Neurol. Centralbl. **15**:685, 1896; cited by Melzner.

174. Karplus: Case Report, Verhandl. d. Gesellsch. f. inn. Med. u. Kinderh. Wien. klin. Wchnschr. **39**:1530, 1926; cited by Rösler.

175. Keith, A.: Malformations of the Heart, Hunterian Lectures, Lancet **2**: 359; 433; 519, 1909; cited by Rösler.

176. —— and MacDonnell, J. J.: Case of Transposition of the Viscera Showing a Potentially Bicameral Heart, Proc. Roy. Soc. Med. (Sect. Med.) **14**:1, 1921.

177. Kienbock, R.: Ueber angeborene Rippenanomalien, Fortschr. a. d. Geb. d Röntgenstrahlen **13**:287, 1909; cited by Rösler.

178. Klebs: Prag. Sammlung, no. 1039; original not accessible; cited by Rösler.

179. —— and Naunyn: Arztl. Korrespondenzbl. f. Bohmen, 1874, vol. II and III; cited by Rösler; original not accessible.

180. Klinz: Dissertatio de praepernaturalibus quibus dam structurae cordis vasorumque illi proximorum. Acta academiae caes, reg. Joseph, Medico chirurgicae vindobonensis, vol. I, p. 228.

181. Knape, W.: Eine seltene Herzmissbildung bei Situs inversus abdominis, Virchows Arch. f. path. Anat. **209**:473, 1912; cited by Laubry and Pezzi.

182. Krausse: Jahrb. f. Kinderh. **62**:35, 1905; cited by Rösler.

183. Kreisch: Ein Fall von hochgradiger Verlagerung des Herzens in die rechte Seite, Bonn Univ. Thesis, 1894; cited by M. & N.

184. Krestin, D.: Congenital Dextrocardia without Transposition of Other Viscera. Acquired Valvular Disease and Auricular Fibrillation, Brit. M. J. **2**: 1223, 1927; cited by Rösler.

185. Krieger, A.: Zur Geschichte der congenitalen Dextrocardie nebst Mitteilung über einen diese Missbildung vortauschenden Krankheitsfall, Inaug. Diss., Berlin, 1880; cited by Foggie, M. & N.; abstr. by Alaux, C.-P.

186. Krokiewicz: Deutsche med. Wchnschr., 1914, p. 1130; cited by Mull.

187. Kronig: Ein Fall von angeborenen Dextrocardie in Folge von Deformation der linken Lunge, Berl. klin. Wchnschr. **35**:230; 446, 1898; cited by Foggie, M. & N., Löwenthal; Schwalbe; abstr. by C.-P.

188. Kuchemeister, F.: Die angeborene vollständige seitliche Verlagerung der Eingeweide des Menschen, 1883; cited by Foggie, M. & N.

189. Kundrat: Ueber die anatomischen Verhältnis bei Transpositio cordis, Ber. d. k. k. Gesellsch. der Aerzte in Wien, Wien. med. Bl. **11**:135; 240; 301, 1888.

190. Kussmaul: Ztschr. f. rat. Med. **26**:99, 1865; cited by Rösler; original not accessible.

191. Lampard, M. E.: Heart Block Associated with Congenital Heart Disease, Arch. Dis. Childhood **3**:212, 1928.

192. de Lange, C.: Angeborene Zystenlunge und agenetische Bronchiektasie Acta pediat. **6**:352, 1927.; cited by Rösler.

193. Langmead, F.: Discussion of Whipham's Case, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **2**:169, 1909; cited by Carpenter.

194. Laubry, C., and Esmein: Note sur la dextrocardie congénitale isolée et sa pathogénie, Bull. et mém. Soc. d. hop. de Paris **44**:281, 1920, cited by M. & R., Rösler.

195. —— and Pezzl, C.: Traité des maladies congénitales du coeur, Paris, J.-B. Baillière et fils, 1921; cited by M. & R. Rösler.

196. Lauri, A.: Destrocardia congenita e stenosi mitralica, cited in Policlinico (sez. prat.) **34**:1760, 1927; cited by Rösler.

197. Leichtenstern: Ref. Krieger; cited by Foggie, M. & N.; abstr. in Krieger's thesis.

198. Lenk, R.: Analyse des Röntgenbildes einer seltenen kombinierten angeborenen Kardiopathie, Wien. med. Wchnschr. **76**:719, 1926; cited by Rösler.

199. Leo, H.: Ueber einen Fall von Dextrocardie, Jahrb. f. Kinderh. **50**:427, 1899; cited by Foggie; M. & N.

200. Leppington, H. M.: Case of Mal- or Transposition of the Heart, with Complete Obliteration of the Gallbladder, London M. Gaz. **15**:228, 1834; cited by M. & N.

201. Leroux, C.; Labbe, R., and Barret, G.: Inversion viscérale totale chez deux frères de 13 et 7 ans, Bull. Soc. de pediat. de Paris **14**:297, 1912; cited by Rösler.

202. LeWald, L. T.: Complete Transposition of the Viscera, J. A. M. A. **84**:261 (Jan. 24) 1925.

203. Lewis, T.: Electrocardiography and Its Importance in the Clinical Examination of Heart Affections, Brit. M. J. **1**:1421, 1479, 1912; Observations on Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber of the Heart, Heart **5**:367, 1913.

204. Lineback, P. E.: An Extraordinary Case of Situs Inversus Viscerum Totalis, J. A. M. A. **75**:1775 (Dec. 25) 1920.

205. Liotta, D.: Situs viscerum inversus complicato a stenosi de l'arteria polmonare e communicazione interventricolare, Riforma med. **43**:869, 1927; cited by Rösler.

206. Loben, F.: Ueber angeborene Rechtslagerung des Herzens bei normalen Situs des Bauchorgane, Fortschr. a. d. Geb. d. Röntgenstrahlen **38**:553, 1928; cited by Rösler.

207. Lochte: Beitrag zur Kenntnis des Situs transversus partialis und der angeborenen Dextrocardie, Beitr. z. path. Anat. u. z. allg. Path. **16**:189, 1894; cited by Foggie, M. & N., C. & B.; Ein Fall von Situs viscerum inversus irreg. ibid. **24**:187, 1898.

164. Host, H. F.: Dextrokardi, Norsk mag. f. lægevidensk. **9**:735, 1911; cited by M. & N.

165. Inches, P. R.: A Case of Dexiocardia, Maritime M. News **3**:63, 1891; cited by M. & N.

166. Indemans, J. W. M.: Dextrocardia congenita or situs cordis inversus, Nederl. tijdschr. f. geneesk. **62**:1405, 1918; cited by Rösler.

167. Jasinski: Ein Fall von angeborener Herzlage in der rechten Brusthälfte, Wien. Med.-Halle **2**:323, 1861; cited by M. & N.

168. Jastrowitz: Dextropositio cordis bei Kyphokoliose mit Differenz des Pulses im beiden Armarterien, München. med. Wchnschr. **56**:793, 1919; cited by Rösler.

169. Jones, H. W.: Types of Dextrocardia, Brit. M. J. **1**:147, 1924.

170. de Jong: Inaug. Diss., Leyden, 1871; cited by Rösler; original not accessible.

171. Josué, O.: Rétrécissement congénital de l'artère pulmonaire avec communication interventriculaire, allodromie par destruction de la branche terminale gauche du faisceau de His, Bull. et mém. Soc. d. hôp. de Paris **43**:408, 1919; cited by Meyer.

172. Joukovsky: Malformation congénital du couer chez les enfants, Petersburg, 1913; Arch. d. mal. du coeur **7**:287, 1914; cited by Rösler.

173. Kalisher, S.: Ueber angeborene Muskeldefect, Neurol. Centralbl. **15**:685, 1896; cited by Melzner.

174. Karplus: Case Report, Verhandl. d. Gesellsch. f. inn. Med. u. Kinderh. Wien. klin. Wchnschr. **39**:1530, 1926; cited by Rösler.

175. Keith, A.: Malformations of the Heart, Hunterian Lectures, Lancet **2**: 359; 433; 519, 1909; cited by Rösler.

176. —— and MacDonnell, J. J.: Case of Transposition of the Viscera Showing a Potentially Bicameral Heart, Proc. Roy. Soc. Med. (Sect. Med.) **14**:1, 1921.

177. Kienbock, R.: Ueber angeborene Rippenanomalien, Fortschr. a. d. Geb. d Röntgenstrahlen **13**:287, 1909; cited by Rösler.

178. Klebs: Prag. Sammlung, no. 1039; original not accessible; cited by Rösler.

179. —— and Naunyn: Arztl. Korrespondenzbl. f. Bohmen, 1874, vol. II and III; cited by Rösler; original not accessible.

180. Klinz: Dissertatio de praepernaturalibus quibus dam structurae cordis vasorumque illi proximorum. Acta academiae caes, reg. Joseph, Medico chirurgicae vindobonensis, vol. I, p. 228.

181. Knape, W.: Eine seltene Herzmissbildung bei Situs inversus abdominis, Virchows Arch. f. path. Anat. **209**:473, 1912; cited by Laubry and Pezzi.

182. Krausse: Jahrb. f. Kinderh. **62**:35, 1905; cited by Rösler.

183. Kreisch: Ein Fall von hochgradiger Verlagerung des Herzens in die rechte Seite, Bonn Univ. Thesis, 1894; cited by M. & N.

184. Krestin, D.: Congenital Dextrocardia without Transposition of Other Viscera. Acquired Valvular Disease and Auricular Fibrillation, Brit. M. J. **2**: 1223, 1927; cited by Rösler.

185. Krieger, A.: Zur Geschichte der congenitalen Dextrocardie nebst Mitteilung über einen diese Missbildung vortauschenden Krankheitsfall, Inaug. Diss., Berlin, 1880; cited by Foggie, M. & N.; abstr. by Alaux, C.-P.

186. Krokiewicz: Deutsche med. Wchnschr., 1914, p. 1130; cited by Mull.

187. Kronig: Ein Fall von angeborenen Dextrocardie in Folge von Deformation der linken Lunge, Berl. klin. Wchnschr. **35**:230; 446, 1898; cited by Foggie, M. & N., Löwenthal; Schwalbe; abstr. by C.-P.

188. Kuchemeister, F.: Die angeborene vollständige seitliche Verlagerung der Eingeweide des Menschen, 1883; cited by Foggie, M. & N.

189. Kundrat: Ueber die anatomischen Verhältnis bei Transpositio cordis, Ber. d. k. k. Gesellsch. der Aerzte in Wien, Wien. med. Bl. **11**:135; 240; 301, 1888.

190. Kussmaul: Ztschr. f. rat. Med. **26**:59, 1865; cited by Rösler; original not accessible.

191. Lampard, M. E.: Heart Block Associated with Congenital Heart Disease, Arch. Dis. Childhood **3**:212, 1928.

192. de Lange, C.: Angeborene Zystenlunge und agenetische Bronchiektasie, Acta pediat. **6**:352, 1927; cited by Rösler.

193. Langmead, F.: Discussion of Whipham's Case, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **2**:169, 1909; cited by Carpenter.

194. Laubry, C., and Esmein: Note sur la dextrocardie congénitale isolée et sa pathogénie, Bull. et mém. Soc. d. hop. de Paris **44**:281, 1920, cited by M. & R., Rösler.

195. —— and Pezzl, C.: Traité des maladies congénitales du coeur, Paris, J.-B. Baillière et fils, 1921; cited by M. & R. Rösler.

196. Lauri, A.: Destrocardia congenita e stenosi mitralica, cited in Policlinico (sez. prat.) **34**:1760, 1927; cited by Rösler.

197. Leichtenstern: Ref. Krieger; cited by Foggie, M. & N.; abstr. in Krieger's thesis.

198. Lenk, R.: Analyse des Röntgenbildes einer seltenen kombinierten angeborenen Kardiopathie, Wien. med. Wchnschr. **76**:719, 1926; cited by Rösler.

199. Leo, H.: Ueber einen Fall von Dextrocardie, Jahrb. f. Kinderh. **50**:427, 1899; cited by Foggie; M. & N.

200. Leppington, H. M.: Case of Mal- or Transposition of the Heart, with Complete Obliteration of the Gallbladder, London M. Gaz. **15**:228, 1834; cited by M. & N.

201. Leroux, C.; Labbe, R., and Barret, G.: Inversion viscérale totale chez deux frères de 13 et 7 ans, Bull. Soc. de pediat. de Paris **14**:297, 1912; cited by Rösler.

202. LeWald, L. T.: Complete Transposition of the Viscera, J. A. M. A. **84**:261 (Jan. 24) 1925.

203. Lewis, T.: Electrocardiography and Its Importance in the Clinical Examination of Heart Affections, Brit. M. J. **1**:1421, 1479, 1912; Observations on Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber of the Heart, Heart **5**:367, 1913.

204. Lineback, P. E.: An Extraordinary Case of Situs Inversus Viscerum Totalis, J. A. M. A. **75**:1775 (Dec. 25) 1920.

205. Liotta, D.: Situs viscerum inversus complicato a stenosi de l'arteria polmonare e communicazione interventricolare, Riforma med. **43**:869, 1927; cited by Rösler.

206. Loben, F.: Ueber angeborene Rechtslagerung des Herzens bei normalen Situs des Bauchorgane, Fortschr. a. d. Geb. d. Röntgenstrahlen **38**:553, 1928; cited by Rösler.

207. Lochte: Beitrag zur Kenntnis des Situs transversus partialis und der angeborenen Dextrocardie, Beitr. z. path. Anat. u. z. allg. Path. **16**:189, 1894; cited by Foggie, M. & N., C. & B.; Ein Fall von Situs viscerum inversus irreg. ibid. **24**:187, 1898.

208. Löwenthal, H.: Ueber angeborene Dextrocardie ohne Situs viscerum inversus; Fehlen der Arteria pulmonalis, mit Ductus botalli als arterielles Gefäss; Lücke im Septum ventriculorum; kleiner linker Ventrikel, Ztschr. f. klin. Med. **41**:130, 1900; cited by Foggie; M. & N.; abstr. by C-P.

209. Löwenthal, Louis: Transposition of the Viscera Occurring in Brothers, Lancet **1**:46, 1909; cited by Neumann, M. & R., Schelenz.

210. Lucchi, A.: Considerazioni sopra un caso di destrocardia congenita a forma rara, Riforma med. **1**:795; 806, 1902; cited by C. & B., M. & R.

211. MacCallum, W. G., and Resnik, W. H.: Cited by Rösler; Personal communication to Rösler.

212. MacLennan, W.: A Case of Dextrocardia Without Displacement of Other Viscera, Brit. M. J. **2**:1314, 1896; cited by Löwenthal, Aufdermauer, Foggie, M. & N.; abstr. in Alaux's thesis.

213. Mandelstamm, M., and Reinberg: Klinische, röntgenologische und elektrokardiographische Untersuchungen über ihre verschiedenen Typen, Ergebn. d. inn. Med. u. Kinderh. **34**:154, 1928.

214. Martin, S.: A Case of Right-Sided Heart, Brit. M. J. **1**:677, 1915; abstr. in Duval's thesis.

215. Maschka: Seltene Missbildungen bei einem neugebornen Kinde, Allg. Wien. med. Ztg., 1862, p. 78; cited by M. & N., Rösler.

216. Mautner, H., and Löwy, M.: Transposition der Aorta oder Persistenz einer rechts-kammerigen Aorta, Virchows Arch. f. path. Anat. **229**:337, 1921; cited by M. & R., Rösler.

217. Mayerhofer: Dislocation des Herzens, Med.-chir. Centralbl. **18**:491, 1883; cited by Rösler.

218. McCrae, J.: A Case of Congenital Atresia of Pulmonary Artery with Transposition of Viscera: A Second Case of Transposition, J. Anat. & Physiol. **11**:28, 1905-1906; cited by Abbott.

219. McIver, L.: A Case of Dextrocardia, Charlotte M. J. **27**:42, 1905; cited by M. & N.

220. McLaughlin, A. I. G.: Congenital and Acquired Dextrocardia: A Case Combining Both Types, Lancet **2**:1064, 1924.

221. Meckel, J. F.: De cordis conditionibus abnormibus, Inaug. Diss., Halle, 1802; abstr. in Krieger's thesis; Arch. f. Anat. u. Physiol., 1826, p. 36; cited by M. & N., Rösler; abstr. in Becker's thesis.

222. Melzner, E.: Angeborener Brustmuskeldefekt und Unfall, Arch. f. klin. Chir. **144**:131, 1927; cited by Rösler.

223. Meyer, P.: Transposition cardio-viscérale compliquées de malformations cardiaques, rétrécissement pulmonaire et communication interventriculaire et de blocage cardiaque complet (Étude des courbes électrocardiographiques et du blocage congénital.), Arch. d. mal. d. coeur **16**:16, 1923; Destrocardie pure isolée avec inversion des cavites cardiaques, ibid. **16**:249, 1923; cited by M. & R., Rösler.

224. Michel, J. F.: Dextrocardia, Med. Rec. **34**:479, 1888; cited by Moffet and Neuhof.

225. Middleton, G. S.: A Case of Congenital Absence of the Left Radius and the Left Thumb, Malformation of the Left Ulna Spinal Curvature, and Complete Displacement of the Heart to the Right, Glasgow M. J. **50**:244, 1898; cited by Foggie, M. & N.

226. Milani, E.: Su due capitoli di radiologia cardiaca: le anomalie congenite, le alterazione del ritmo del cuore, Radiol. med. **15**:693, 1928; cited by Rösler.

227. Miller, A. J.: Congenital Heart Disease with Partial Situs Inversus, Absence of Inferior Vena Cava and Other Anomalies, Am. J. Path. **1**:46, 1925; cited by Sakurai.

228. Moellenbrock: Miscellanea Curiosa, 1671, cases 76, 139; cited by M. & N., Breschet, Aufdermauer, Foggie; abstr. in Krieger's thesis; original not accessible.

229. Moffett, R. D., and Neuhof, S.: Congenital Dextrocardia with Patent Interventricular Septum with Fluoroscopic and Electrocardiographic Examination, Am. J. Dis. Child. **10**:1 (July) 1915; cited by M. & N., M. & R.

230. Mohr: Demonstration eines Falles von Situs inversus totalis mit Elektrokardiogramm, Verein der Aerzte in Halle, München. med. Wchnschr. **59**:387, 1912; cited by C-P.

231. Mönckeberg, J. C.: Untersuchungen über das Atrioventrikularbundel im menschlichen Herzen, Jena, G. Fischer, 1908; Herzmissbildungen. Ein Atlas angeborener Herzfehler in Querschnitten mit besonderer Berücksichtigung des Atrioventrikularsystems, Jena, G. Fischer, 1912; Verhandl. d. deutsch path. Gesellsch., 1913, p. 228; Zentralbl. f. Herz- u. Gefässkr. **7**:272, 1915; Ergebn. d. allg. Path.. u. path. Anat. **19**:328, 1921; Die Missbildlungen des Herzens, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. II (Herz und Gefässe), p. 16; cited by M. & R., Rösler.

232. Monclavi, L.: Un caso di cianosi con stenosi congenita della pulmonare, destrocardia con situs viscerum inversus, Pediatria **28**:907, 1920; cited by Meyer.

233. Monks, E. H.: Congenital Dextrocardia with Patent Ductus Ovale: Necropsy at 9 Months, Am. J. Dis. Child. **12**:233 (Sept.) 1916; cited by Laubry and Pezzi.

234. Morgan, H. J.: The Auriculo-Ventricular Node in a Malformed Heart with Remarks on Its Nature, Connexions, and Distribution, J. Anat. & Physiol. **47**:439, 1913; cited by Rösler.

236. Mosler, F.: Ueber congenital Dextrocardie, Berl. klin. Wchnschr. **3**:221, 1866; Ein Fall von congenitaler Dextrocardie, Deutsche med. Wchnschr. **3**:301, 1877; cited by Vehsemeyer, Aufdermauer, Foggie, Lochte, M. & N., M. & R., Rösler; abstr. in Alaux, Becker, C-P.'s theses.

237. Mull, W.: Beitrag zur Kenntnis des Situs viscerum inversus, Deutsche Ztschr. f. Chir. **199**:127, 1926.

238. Muller, H.: Beitr. z. path. Anat. u. allg. Path., 1912, vol. 51, no. 3; abstr. by C-P.

239. Nagel, M.: Beiträge zur Kasuistik und Lehre von der angeborenen reinen Dextrokardie, Deutsches Arch. f. klin. Med. **96**:552, 1909; cited by M. & N., C. & B., M. & R., Rösler.

240. Neuhof, S.: Case of Familial Congenital Dextrocardia, J. A. M. A. **60**:1064 (April 5) 1913.

241. Neumann, E.: Ueber einen Fall von Dextrokardie. Ein Beitrag zur Lehre des Situs transversus partialis, Inaug. Diss., Marburg, 1906; cited by M. & N., Foggie, Nagel; abstr. by C-P.

242. Neumann, W.: Ueber Dextroversio cordis und ihren Einflüss auf das Elektrokardiogramm, Deutsche med. Wchnschr. **38**:1920, 1912.

243. Nicolai, G. F.: Das Elektrocardiogramm bei Dextrocardie und anderen Lageveränderungen des Herzens, Berl. klin. Wchnschr. **48**:51, 1911.

244. Niesel: Ueber einen Fall von Dextrocardie, Deutsche med. Wchnschr. **16**:499, 1890; same as Sandhop case; cited by Foggie, M. & N., Löwenthal, Vehsemeyer; abstr. by C-P., Alaux.

245. Northrup, W. P.: Reptilian Heart or Rudimentary Auricles, Septum, Rudimentary Ventricular Septum, Obliterated Pulmonary Orifice and Trunk, Absence of Pulmonary Veins, Absence of Mitral Orifice, Anomalous Veins and Arteries, Proc. New York Path. Soc., 1888; cited by Holt.

246. Oberwarth, E.: Ueber angeborene Agenesie einer Lunge, Jahrb. f. Kinderh. **60**:383, 1904; cited by Rösler.

247. Ochsenius, K.: Familial Situs Inversus, Monatschr. f. Kinderh. **19**:27, 1920; cited by M. & R.

248. Otto, A. W.: Seltene Beobachtungen zur Anatomie, Physiologie und Pathologie der Gehörorganen, Breslau, 1816, p. 95; Neue seltene Beobachtungen zur Anatomie, Physiologie und Pathologie der Gehörorganen, 1824, p. 47; Neues Verzeichnis der anatomische Sammlungen z. Breslau, 1841, p. 108, no. 733; cited by Löwenthal, Pol., M. & R.; abstr. in Krieger and Becker's thesis.

249. Owen, S. A.: A Case of Complete Transposition of the Viscera Associated with Mitral Stenosis Including a Description of the Electrocardiographic Tracings, Lancet **2**:113, 1912.

250. Paganuzzi: Gior. veneto di sc. med. **27**:3, 1877; original not accessible; cited by Rösler.

251. Pal, J.: Angeborene Dextrokardie (Dextroversio cordis) mit Aorten-Stenose, Wien. med. Presse **48**:809, 1907; Zur Pathogenese der Dextroversio cordis (R. Paltauf), Zentralbl. f. Herz- u. Gefässkrankh. **11**:249, 1919; same as Gruss' case; cited by Foggie, C. & B., M. & R.; abstr. by C-P.

252. Paltauf, R.: Dextrocardie und Dextroversio Cordis, Wien. klin. Wchnschr. **14**:1032, 1901; see Bamberger and Pascheles; cited by Foggie, M. & N., M. & R.; abstr. in Alaux's thesis.

253. Pappenheimer, A. M.: Complete Transposition of the Viscera with Associated Developmental Defect of the Heart, Proc. New York Path. Soc. **13**:1, 1913.

254. Parkinson, P.: A Case of Dextrocardia: Reports of the Society for the Study of Disease in Children, 1903, vol. 3, p. 213; cited by M. & N.

255. Parsons-Smith, B.: A Note on Dextrocardia, Complete and Incomplete: With Four Illustrative Cases, Lancet **2**:1076, 1919.

256. Pascheles, W., and Paltauf, R.: Ein Fall von Dextrocardie, Wien. klin. Rundschau **11**:473, 1897; see Bamberger, 1888; cited by M. & N.

257. Pernkopf, E.: Der partielle Situs inversus der Eingeweide beim Menschen, Ztschr. f. Anat. u. Entwicklungs Geschichte **89**:577, 1926; cited by M. & R.

258. Peters: Inaug. Diss., Bonn, 1924; original not accessible; cited by Rösler.

259. Petit, A., and Ravaut: Dextrocardie isolée d'origine congénitale, Gaz. d. hôp. **71**:293, 1898; Bull. et mém. Soc. méd. d. hôp. d. Paris **15**:195, 1898; cited by Foggie, M. & N., Gossage; abstr. in C-P.'s thesis.

260. Plumier-Clermont: Scalpel **77**:811, 1924; cited by Rösler.

261. Pol: Isthmusatresie und Dextrocardie (Dextroversio Cordis). Recurrende Endocarditis, Verhandl. d. deutsch. path. Gesellsch. **20**:392, 1925; see Bahn: cited by M. & R., Rösler.

262. Ponfick: Ein Fall von angeborener primärer Atrophie der rechten Lunge, Virchows Arch. f. path. Anat. **1**:633, 1870; cited by Rösler.

263. Ponzio: Situs viscerum inversus parziale, Radiol. med. **13**:208, 1926; cited by Rösler.

264. Pope, C.: A Case of Transposition of Heart, Lancet **2**:9, 1882; cited by Foggie, C. & B., M. & R.

265. Popovici-Lupa, M.: Spitalul **48**:175, 1928.

266. Potter, G. W.: Congenital Malformation of Heart with Malposition of Certain Viscera and Absence of Spleen, J. A. M. A. **47**:363 (Aug. 4) 1906; cited by M. & N.

267. Potts, R. H., and Ashman, R.: A Case of Dextrocardia with Right (Functional Left) Ventricular Predominance, Ventricular Ectopic Beats and Retrograde Conduction, Am. Heart J. **2**:152, 1926; cited by Rösler.

268. Prag: Case Presentation, Klin. Wchnschr. **3**:89, 1924.

269. Prendergrass: 1927; no reference; cited by Rösler.

270. Quadrone, C.: Attorno ad un caso di destrocardia congenita pura con endocardite acquisita, Riv. crit. di clin. med. **6**:89, 1905; cited by Scandola.

271. Rach, E.: Röntgendiagnostik der kindlichen Lungenerkrankungen, Ergebn. d. inn. Med. u. Kinderh. **32**:464, 1927.

272. Ratner, B.; Abbott, M. E., and Beattie, W. W.: Rare Cardiac Anomaly: Cor Triloculare Biventriculare in Mirror-Picture Dextrocardia with Persistent Omphalo-Mesenteric Bay, Right Aortic Arch and Pulmonary Artery Forming Descending Aorta, Am. J. Dis. Child. **22**:508 (Nov.) 1921; cited by Rösler.

273. Reddingius, R. A.: Ein geval van dextrocardie mit transpositie van alle groote vaten, Weeklaad v. h. tijdschr. v. geneesk., 1889, no. 15; ref. Centralbl. f. klin. Med., 1889, no. 35, p. 611; cited by Foggie, M. & N.; abstr. in Becker's thesis.

274. Reggiani, G.: Di una rara malformazione cardiaca con cianosi parossistica in soggetto di 73 giorni, Clin. pediat. **7**:583, 1925; cited by Rösler.

275. Reid, D. M.: Transposition of the Viscera Occurring in Brothers, Lancet **1**:717, 1909; cited by Rösler, M. & R.

276. Reinberg, S. A.: Congenital Genuine Dextrocardia with Report of a Case, Ann. Roentgenol. **1**:213, 1922.

277. Reinhardt: Ein Fall von Situs viscerum inversus totalis bei Zwillingen (Rekruten), Deutsche milit.-ärztl. Ztschr. **41**:931, 1912; cited by M. & R. Rösler.

278. Reuss, A.: Angeborene Scoliosis, Torticollis, Dextrocardia, Wien. Gesellsch. f. Kinderh., Nov. 30, 1927; Wien. med. Wchnschr. **78**:29, 1928; cited by Rösler.

279. Rieder: Ann. d. städt. deutsche milit.-ärztl. Ztschr. **41**:932, 1912; original not accessible; cited by Rösler.

280. Rindfleisch: Lehrbuch der pathologischen Gewebelehre, zur Einführung in das Studium der pathologischen Anatomie, Leipzig, Wilhelm Engelmann, 1871; city by Laubry and Pezzi.

281. Riolan, J.: Anthropographia, 1649; cited by Otto, M. & N.

282. Rivet and Girard: Bull. et. mém. Soc. anat. de Paris **87**:181, 1912; cited by Rösler.

283. Robinson, A. R.: Transpositio Cordis with Abnormal and Imperfect Development, There Being Only One Auricle and One Ventricle, Bull. New York Path. Soc. **4**:48, 1881; cited by Foggie, M. & N., M. & R., C-P.

284: Roelfs: Inaug. Diss., Marburg, 1923; cited by Rösler; original not accessible.

285. Rogi, E.: Storia di una trasposizione dei visceri, Sperimentale **45**:376, 1880; cited by Rösler.

286. von Rokitansky, C. F.: Die Defecte der Scheidewände des Herzens, Vienna, W. Braunmüller, 1875, p. 5; cited by Kundrat.

287. Romberg, E. G., and White, P. D.: Heart Block and Congenital Heart Disease, Boston M. & S. J. **190**:591, 1924.

288. Rösler, H.: Beiträge zur Lehre von der angeborenen Herzfehlern, ueber die angeborene isolierte Rechtslage des Herzens, Wien. Arch. f. inn. Med. **19**: 505, 1930.

289. Royer, B. F., and Wilson, J. D.: Incomplete Heterotaxy with Unusual Heart Malformations: Case Report, Arch. Pediat. **25**:881, 1908.

290. Sakurai, M.: Ein Fall von Situs inversus partialis mit der Missbildung des Herzens, Sei-I-Kwai M. J. **46**:9 (March) 1927.

291. Samoiloff, A.: Vorzüge der mehrfachen Ableitung der Herzströme bei Elektrokardiogramm-Aufnahmen, illustriert in zwei Bispielen, Arch. f. d. ges. Physiol. **153**:196, 1913; Elektrocardiogramm bei Situs viscerum inversus, Zentralbl. f. Herz- u. Gefässkr. **6**:201, 1914; cited by C. & B.

292. Sandhop, M.: Ein Fall von kongenitaler Dextrokardie ohne Situs viscerum transversus der übrigen Organe (see Niesel's case), Griefswald Univ. Thesis, 1890; cited by Nagel, M. & N.

293. Sandifort, E.: Observationes anatomico-pathologicae, 1782, vol. 4, chapter 6, section 55; original not accessible; cited by Rösler.

294. Sapegno, M.: Pathologia del fascio atrioventriculare, Path. riv. quindici **2**:175, 1909-1910; cited by Rösler.

295. Sato, S.: Ueber die Entwicklung der atrio-ventriculär Klappen und der Pars membranacea unter Berücksichtigung zugehöriger Herzmissbildungen, Anat. Hefte **50**:193, 1914; cited by Rösler.

296. Scandola, C.: Sopra un caso di destrocardia pura congenita, Gazz. d. osp. **30**:1065, 1909; cited by C. & B., M & N.; abstr. by C-P.

297. Shapiro, P. F.: Detorsion Defects in Congenital Cardiac Anomalies, Arch. Path. **9**:54 (Jan.) 1930.

298. Scheele: Zwei Fälle von vollständigem Situs viscerum inversus, Berl. klin. Wchnschr. **12**:403, 418, 1875; cited by Blumenfeldt.

299. Schelenz, C.: Ein neuer Beitrag zur Kenntnis des Situs viscerum inversus partialis, Inaug. Diss., Gottingen, 1909; Berl. klin. Wchnschr. **46**:788, 1840, 1909; cited by M. & N.; abstr. by C-P.

300. Schlesinger, H.: Zur Lehre vom angeborenen Pectoralis-Rippen Defect und dem Hochtande der Scapula, Wien. klin. Wchnschr. **5**:13; 25, 1900; cited by Rösler; see Kienbock's case.

301. Schmid-Monnard: Vorstellung eines Falles von Dextrocardie ohne Situs viscerum inversus, München. med. Wchnschr. **41**:584, 1894; cited by Löwenthal, M. & N.

302. Schmilinsky: Case Presentation: Dextrocardia with Persistent Ductus Arteriosus Botalli, Deutsche med. Wchnschr. **26**:194, 1900; cited by Nagel, Foggie, M. & N.

303. Schneider: Situs viscerum inversus bei einem 18 jährigen Jünglinge, Wien. klin. Wchnschr. **21**:1341, 1908; cited by Rösler.

304. Schott: Ueber congenitale Dextrocardie, Therap. Monatsh. **5**:280, 1891; cited by Foggie, M. & N.; abstr. in Alaux's thesis.

305. Schroetter, L.: Beitrag zur Kenntnis der Lageveränderung des Herzens, Med. Jahrb. **20**:189, 1870; Ueber angeborene Dextrocardie, Berl. klin. Wchnschr. **24**:448, 1887; Ueber Dextrocardie, Wien. med. Presse **35**:30; 69, 1894; cited by Foggie, M. & N., C. & B., Rösler; abstr. in Alaux, Löwenthal, Becker's thesis.

306. Schuessler, O.: Dextrocardia with Supernumerary Ribs and Vertebra, Deutsche med. Wchnschr. **46**:657, 1920.

307. Schultze, B. S.: Ein Fall von Heterotaxia der Bauch und Brusteingeweide und wahrschleinlichem Offenstehen des Foramen ovale nebst allgemeinen Bemerkungen über Genese dieser beiden Bildungsfehler, Virchows Arch. f. path. Anat. **22**:209, 1861.

308. Seitz, C.: Ein seltene Missbildung der Thorax, Virchows Arch. f. path. Anat. **98**:335, 1884.

309. Senac, J.-B.: Traité de la structure du coeur, de son action et de ses maladies, Paris, 1749; cited by Jones, M. & R.

310. Senator: 1899; cited by Löwenthal, Aufdermauer, C-P.

311. Serres: Recherches d'anatomie transcendante et pathologiques, Paris, 1832; cited by Laubry and Pezzi; original not consulted.

312. Seyffert: Arch. f. Gynäk. **112**:413, 1920; cited by Rösler.

313. Shaw, E., and Blake, H. K.: Transposition of the Abdominal Viscera: Reversal of the Heart Chambers with Left-handed Heart, Am. J. Dis. Child. **28**:204 (Aug.) 1924; cited by M. & R.

314. Sheffield, H. B.: Ein Fall von Dextrokardie, Centralbl. f. Kinderh. **11**:37, 1906; cited by Rösler.

315. Sikora: Un cas de maladie bleue avec transposition totale des viscères, Soc. méd. Hôp. de Paris, 1899; cited by Meyer.

316. Silberstein, A.: Angeborene Thoraxdefecte, Ztschr. f. orthop. Chir. **15**:24, 1905-1906; cited by Rösler.

317. Smith, A. A.: The Heart on the Right Side Without Transposition of the Other Viscera, New York M. J. **27**:512, 1878.

318. Smith, J.: Very Singular Position of the Heart with the Dissection, Phila. Med. Mus. **4**:43, 1808; cited by Rösler.

319. Sobierajczyk, A.: Zur Casuistik der Dextrocardie nebst Beschreibung eines dies bezüglichen neuen Falles, Berlin, 1896; cited by M. & N.; abstr. by C-P.; see Vehsemeyer's case.

320. Spitzer, A.: Ueber Dextroversion, Transposition und Inversion des Herzens und die gegenseitige Larvierung der beiden letzteren Anomalien, Virchows Arch. f. path. Anat. **271**:226, 1929; see Rösler case 1.

321. Steiner, T.: Ueber angeborene und erworbene Dextrokardie nebst einem Fall von erworbener Dextrokardie infolge rechtseitiger Schrumpfungspleuritis, Inaug. Diss., Berlin, 1896; cited by Löwenthal.

322. Steudener, F.: Angeborene Stenose des Ostium arteriosum pulmonale mit vollstandigen Mangel der Ventrikelsscheidewand sowie gleichzeitig vorhandenem Situs transversus, Deutsche Klin., 1870, no. 1; cited by Wehn.

323. Stoerk, E.: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **10**:12, 1911; Wien. klin. Wchnschr. **24**:222, 1911; abstr. by C-P.; cited by Rösler.

324. Stokes, A.: Abnormal Position of the Heart and Great Blood Vessels Associated with Transposition of the Viscera, J. Anat. & Physiol. **43**:301, 1909.

325. Stolkind, Y. Y.: Clinical Picture of Dextrocardia and Dextroversio Cordis, Prakt. Vrach. **15**:69, 83, 1916; original abstr. in C-P.'s thesis not accessible; cited by Rösler.

326. Stone, A. K.: Cardiac Displacement, Boston M. & S. J. **150**:29, 1904; cited by C. & B.

327. Storch, W.: Monatschr. f. Kinderh. **2**:1, 1903; cited by Carter and Howland.

328. Storen, E.: Et tilfælde af medfødt dextrokardi (Dextrocardie congénitale chez un adulte), Norsk mag. f. lægevidensk. **9**:93, 1894; cited by Vehsemeyer, M. & N., Rösler.

329. Strothmann, H.: Ueber einen Fall von isolierter komplizierter Dextrokardie mit korrigierter Transposition der grossen Gefässe, Deutsches Arch. f. klin. Med. **163**:76, 1929.

330. Süssmann, L.: Beitrag zur Casuistik der angeborenen Rechtslagerung des Herzens (aus dem allgemeinen Krankenhause zu Bamberg), München. med. Wchnschr. **34**:991, 1014, 1887; cited by Löwenthal, Foggie, M. & N.

331. Tate, R. G. H.: A Case of Transposition of the Heart, J. Roy. Army M. Corps **8**:434, 1907; cited by Foggie, M. & N.

332. Theocare, K. C.: Title in Greek, Galenos, 1881, p. 436; 1882, p. 4; cited by Rösler.

333. Tison, J.: Un cas de malformations multiples décelées par la radiographie, Bull. et mém. Soc. d. radiol. méd. de France **6**:58, 1914; cited by C. & B.

334. Torrez: Mémoires present, 1750, vol. 1, p. 136; Abhandl. a. d. Acad. d. Wissensch. z. Paris **2**:156, 1754; original not consulted; abstr. by Krieger.

335. Toy, W. B., and Ellis, A. G.: Transposition of Viscera with Multiple Malformations, J. A. M. A. **74**:322 (Jan. 31) 1920.

336. Upson, W. O.: Transposed Viscera, Am. J. Roentgenol. **8**:385, 1921.

337. Valleix: Bull. Soc. d'anat. de Paris, 1839; cited by Wehn; original not consulted.

338. Vandeput: J. méd. de Bruxelles **17**:37, 1912; cited by M. & N.

339. Vanderwelde, P.: J. méd. de Bruxelles **17**:37, 1912; cited by M. & N.; abstr., in C-P.'s thesis.

340. —— and Cantineau, G.: Dextrocardie congénitale, J. méd. de Bruxelles **16**:223, 1911; cited by M. & N., C. & B.

341. Vaquez, H., and Donzelot: Dextrocardie et dextroversion, Presse méd. **28**:41, 1920; cited by M. & R.

342. Vehsemeyer: Ein Fall von congenitaler Dextrokardie zugleich ein Beitrag zur Verwerthung der Röntgenstrahlen der innerten Medicin, Deutsche med. Wchnschr. **23**:180, 1897; Sobierajczyk Case; cited Foggie; C. & B.; M. & N., M & R., Rösler.

343. Virchow, R.: Ein Fall von Transposition der Eingeweide beim Neugeborenen, Virchows Arch. f. path. Anat. **22**:425, 1861.

344. Vittinghoff: Inaug. Diss., Marburg, 1897; cited by Rösler; original not accessible.

345. Wagner, B.: Zur Kenntnis der erworbenen und angeborenen Rechtslage des Herzen, Inaug. Diss., Rostock, 1902; cited by Foggie, M. & N.; original not accessible.

346. Wechsberg, F.: Ueber eine seltene Form von angeborener Missbildung der Lunge, Centralbl. f. allg. Path. u. path. Anat. **11**:593, 1900; cited by Rösler.

347. Wehn, J.: Beiträge zur Heterotaxie der Eingeweide, Inaug. Diss., Wurzburg, 1882; cited by Foggie, M. & N.; abstr. in Alaux's thesis.

348. Weill, E.; Gardere, C.; Wertheimer, P., and Bernheim, M.: Malformations congénitales multiples, agénésie partielle du rocher avec absence du conduit auditif externe et rétrécissement de l'aorte, Arch. d. mal. du coeur **27**:273, 1924; cited by Rösler.

349. Weinberger, M.: Seltener Fall von Verlagerung des Herzens in die rechte Brusthöhle, Wien. klin. Wchnschr. **14**:129, 1901; Mitt. d. Wien. Gesellsch. f. inn. Med. u. Kinderh. **1**:2204, 1902; Zur Klinik der angeborenen isolierten Dextrokardie und Dextroversio cordis, Zentralbl. f. Herz- u. Gefässkr. **11**:121, 137, 1919; cited by Foggie, M. & N., M. & R., Rösler.

350. Welsch, K.: Ein Fall von Mangel der rechten Lunge, Frankfurt. Ztschr. f. Path. **36**:192, 1928; cited by Rösler.

351. Wendling, L.: Ein Fall von angeborener Dextrokardie, Med. Bl. **26**:563, 1903; cited by Foggie, M. & N.

352. Wenner, O.: Beiträge zur Lehre der Herzmissbildungen, Virchows Arch. f. path. Anat. **196**:127, 1909; cited by C. & N., M. & R.; abstr. by C-P.

353. von Werdt, F.: Zur Kenntnis des Situs inversus und der mit demselben häufig verbundenen Anomalien im Bereiche der grossen Abdominal-Venen, Arch. f. mikr. Anat. **95**:37, 1921.

354. Weygandt: Verhalten des Gehirns bei Situs viscerum transversus, Neurol. Centralbl., 1904, p. 487; cited by Nagel.

355. Whipham, T. R.: Transposition of the Viscera, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **2**:169, 1909; cited by Carpenter.

356. White, P. D.; Eustin, R. S., and Kerr, W. J.: Congenital Heart Block, Am. J. Dis. Child. **22**:299 (Sept.) 1921.

357. Whyte, G. D.: Reports on Medical and Surgical Practice in the Hospitals and Asylums of the British Empire, Brit. M. J. **2**:198, 1910.

358. Wigger, C.: Angeborene Lückenbildung in der Brustkorbwandung, Zentralbl. f. Gynäk. **5**:263, 1928; cited by Rösler.

359. Wilks, S., and Moxon, W.: Lectures on Pathologic Anatomy, London, 1889, p. 109; cited by Rösler.

360. Willius, F. A.: Congenital Dextrocardia, Am. J. M. Sc. **157**:485, 1919.

361. Wilson: Phil. Tr. London **2**:396, 1789; cited by Rösler; original not accessible.

362. Wilson, J. G., and Grant, R. T.: A Case of Congenital Malformation of the Heart in an Infant Associated with Partial Heart Block, Heart **12**:295, 1925-1926.

363. Wilson, F. N.: Discussion, Tr. A. Am. Physicians **45**:168, 1930.

364. Winokurow: Ztschr. f. orthop. Chir., vol. 47; Verhandl. d. orthop. Gesellsch., p. 381; cited by Rösler; original not consulted.

365. Wolfshöfer: Arch. d. med. Correspondenzbl. (ref. incomplete); cited by Scheele; original article not accessible.

366. Wright, J. H., and Drake, A. K.: A Case of Extreme Malformation of the Heart, Tr. A. Am. Physicians **18**:272, 1903; cited by M. & N.

367. Würzburger Pathologisches Institute: 1824; case cited by Mösler, Schroetter, Vehsemeyer, M. & N.

368. Van Zant, C. B.: A Case of Congenital Dextrocardia, Cincin. Lancet-Clinic **13**:158, 1884; cited by Aufdermauer.

369. von Ziemssen, H.: Ann. d. städt. allg. Krankenh. zu München (ref. incomplete); cited by Vehsemeyer, Becker, M. & N.

370. —— and Rieder, H.: Die Röntgenographie in der inneren Medizin, 1902, plate B6; cited by Rösler.

Book Reviews

RÖNTGENDIAGNOSTIK DER GALLENBLASE. (RADIOLOGISCHE PRAKTIKA; BAND XVII). By DR. F. EISLER and DR. G. KOPSTEIN. Price, 18.60 marks. Pp. 153, with 151 illustrations. Leipzig: Georg Thieme, 1931.

In this monograph the authors have made an exhaustive study of the literature on cholecystography. Their discussions and conclusions are based on studies of their own material, which represents about 10,000 cases. The subject is presented in a practical manner and is abundantly illustrated.

A brief history of the development of cholecystography is given. This is followed by a short discussion on the anatomy and physiology of the extrahepatic biliary system.

The intravenous, oral, intraduodenal and rectal methods of administering gallbladder dye are described in detail, and a comparison is made. The authors prefer the oral method. Their method of administration of the dye (Iodotetragnost, Merck) is given in detail. The first roentgenogram is taken from twelve to fourteen hours after the ingestion of the dye. A drink containing two or three egg yolks is then given and another x-ray plate taken one-half hour later. Films 30 by 40 cm. are used; the patient is placed prone on a Bucky diaphragm; the dosage is from 70 to 80 peak kilovolts, 60 milliamperes, 0.2 second; the patient is placed so that the anterior axillary line at the eleventh rib is at the middle of the lateral edge of the film.

Reactions to the dye, the authors believe, are more numerous with the oral method than following intravenous administration, but are never so severe as with the latter. They believe that the amount of dye over 3 Gm. should be given cautiously. Contraindications to giving gallbladder dye are cardiac decompensation, hyperthyroidism, anemia, chronic nephritis, cirrhosis of the liver, diabetes and icterus with fever.

Cholecystographic findings are next discussed. Deformities of the gallbladder are divided into two classes, namely, true or organic, and false deformities as the result of pressure from without. As to the size of the normal gallbladder, the authors believe that there is no definite way of measuring. The ability of the gallbladder to empty is used as an index as to whether or not the size is pathologic. The various positions the gallbladder may take are described. The intensity of the gallbladder shadow depends on too many factors to be in itself of diagnostic value. The authors believe that nonvisualization when no hepatic disease is present means obstruction to the cystic duct or changes in the walls of the gallbladder. One exception is, however, a large gallbladder which in itself casts a shadow.

Gallstones are divided into four types, namely, opaque stones with or without visualization of the gallbladder, and nonopaque stones with or without visualization of the gallbladder. The cholecystographic findings relative to these types of stones are discussed in detail.

Gallbladder shadows persisting for as long as forty-eight hours have been observed. Whether this is due to obstruction or to repeated filling can be answered by giving the egg drink and observing the change in the size of the shadow.

The authors believe that a diagnosis of adhesions of the gallbladder cannot accurately be made.

The sources of shadows simulating a dye-filled gallbladder are discussed and illustrated. The differential diagnosis can be made by observations following the egg drink.

It is the authors' belief that the rate of elimination of the gallbladder dye as an index for liver function is not practicable.

Cholecystography in children has not been done in a large enough series by the writers to allow drawing of definite conclusions.

The sources of error in cholecystography are discussed. Chiefly they are: too long a period between administration of the dye and the taking of the first roentgenogram, faulty position of the patient on the film, and time of exposure to the x-rays.

The final two chapters are devoted to roentgen findings of the extrahepatic biliary system, such as fistula and air as seen after the administration of barium in gastro-intestinal studies; also the value of gallbladder dye in hepatography.

DIE KRANKHEITEN DES STOFFWECHSELS UND IHRE BEHANDLUNG. By E. GRAFE. Cloth. Price, 29.60 marks. Pp. 518. Berlin: Julius Springer, 1931.

This book is volume XIV of a series of monographs prepared under the aegis of *Klinische Wochenschrift* for the guidance of the practitioner. The author, E. Grafe, director of the Medical Clinic of the University of Würzburg, is a foremost authority on metabolism. His scientific contributions in this field are important, and his ability as a teacher is equally recognized. The subject, diseases of metabolism and their management, constitutes the center field of internal medicine, and its interest to the practitioner has been happily augmented of recent years by a series of discoveries of the utmost importance for successful treatment. This applies especially to diabetes, and this disease is accordingly given special attention. The chapters on diabetes mellitus constitute, in the reviewer's opinion, the most instructive exposition of this complex disease that has appeared since the publication, in Nothnagel's "System," of Naunyn's famous treatise.

The section on diabetes contains a particularly valuable, concise and judicial review of the theories as to the action of insulin which will be appreciated by those who have been staggered by the enormous and confusing literature that has grown around this subject. On the whole, however, theory is subordinated to practical consideration and is discussed only so far as it bears on the understanding of the nature and treatment of the various disorders considered.

A list of important general articles at the end of each section provides the reader with ample guides to the literature; otherwise, references are limited to articles which the author considers to be of special significance.

The larger subdivisions of the book cover nutrition, obesity, diabetes and gout. Smaller sections are devoted to the avitaminoses, diabetes insipidus, alkaptonuria, cystinuria and stone formation.

The writing is excellent and admirably concise, and the treatment of each subject is soundly critical, with careful distinction drawn between fact, hypothesis and fancy.

BLUTUNG UND FLUOR. By PROF. DR. MED. HANS RUNGE, Oberarzt der Universitätsfrauenklinik Kiel. Mit einem Vorwort von PROF. DR. MED. R. SCHRÖDER, Direktor der Universitätsfrauenklinik Kiel (Band IX der Sammlung "Medizinische Praxis," herausgegeben von L. R. GROTE, A. FROMME und K. WARNEKROS). Price, 8 marks. Pp. 108. Dresden: Theodor Steinkopff, 1930.

The author considers genital bleeding and discharge as two of the most frequent and important symptoms which the practitioner and gynecologist encounter. He introduces the monograph with a consideration of some of the physiologic and cyclic changes in the ovary and the uterus and discusses briefly some of the results of the study of the hormones. Menstrual bleeding—normal, profuse, long-continued, frequent and infrequent—is given a place.

Atypical continued bleeding, the source and the pathologic basis are given thoughtful consideration.

Obstetric hemorrhages are not taken up extensively as they do not have a legitimate place in this presentation.

The management and treatment, including the applicability of hormone therapy, are considered. The author expresses the opinion that the latter is still in flux, and the indications, methods and results are still undecided.

The smaller part deals with fluor or discharge, and this topic is also preceded by a discussion of the physiology.

The value of the recognition of the source and the causative factors is emphasized. The indications and methods of treatment are considered, and special mention is made of the liability to the occurrence of leukorrhea in association with pregnancy.

This monograph is one of a series that deals with various subjects of interest to practitioners and is a valuable part of the set as it brings up-to-date information forward in a concise readable form for the practitioner of gynecology. The value of the publication is enhanced by a number of diagrams and illustrations of the various conditions presented in the text.

HEART DISEASE. By PAUL DUDLEY WHITE, M.D., Instructor in Medicine, Harvard Medical School; Physician, Massachusetts General Hospital, Boston. Price, $12. Pp. 930, with 119 illustrations. New York: The Macmillan Company, 1931.

The author divides the subject into four divisions. The first is concerned with the examination of the patient and the analysis of the symptoms and signs. The second discusses the etiologic types and causes of heart disease. The third considers the structural changes, and the fourth deals with the disorders in function. The order of the last three divisions is based on the present trend in cardiac diagnosis.

The first division is one of the most important from the standpoint of the beginner, and may be read with interest and profit by those with special knowledge in the field. The section on the roentgenologic and electrocardiographic methods of examination are well done. Approximately ninety pages are devoted to the last subject, and many of the most important alterations in the electrocardiogram are illustrated by curves.

The discussion of the three remaining divisions is a conservative presentation of the newer concept of heart disease. The consideration of rheumatic heart disease as such gives a much more comprehensive point of view then has heretofore been expressed in books of this kind. The continuity of the text might possibly have been improved had the arteriosclerotic form of heart disease been discussed in the same manner. Angina pectoris may be cited as an example. This condition is considered with the disorders in function, yet it is one of the most characteristic manifestations of diseases of the coronary artery. This is, however, of minor consequence, compared to the many admirable features of the book. The illustrations were carefully selected, and the author has added considerably to the interest of the readers by including in certain chapters quotations from the original work which represent milestones in the development of knowledge of heart disease. The bibliography is another feature worthy of special mention. The book fulfils a definite need, and is heartily recommended to all interested in heart disease.

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, Editor-in-Chief, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the Association when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright but, as a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $7.00; Canadian, $8.50; foreign, $8.50. Single copies, 15 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75. Single copies, 55 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75. Single copies, 55 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.60; foreign, $9.75. Single copies, 75 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, $8.00; Canadian, $8.60; foreign, $8.75. Single copies, 85 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.60; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original contributions in the field of pathology, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.60; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.60; foreign, $6.75. Single copies, 75 cents.

QUARTERLY CUMULATIVE INDEX MEDICUS—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $12.00; Canadian, $13.50; foreign, $12.75.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO

CONTENTS

PAGE

THE CAUSATION AND PREVENTION OF CONGENITAL HEART DISEASE. WILLIAM D. REID, M.D., BOSTON 721

TUBERCULOSIS IN MEDICAL AND COLLEGE STUDENTS. H. W. HETHERINGTON, M.D.; F. MAURICE MCPHEDRAN, M.D.; H. R. M. LANDIS, M.D., AND EUGENE L. OPIE, M.D., PHILADELPHIA 734

INFECTIVE NEURONITIS: REPORT OF A CASE WITH AUTOPSY OBSERVATIONS. HARRY G. JACOBI, M.D., NEW YORK 764

THE CUTANEOUS HISTAMINE REACTION AS A TEST FOR COLLATERAL CIRCULATION IN THE EXTREMITIES. G. DE TAKÁTS, M.D., CHICAGO 769

INTESTINAL OXYGENATION IN IDIOPATHIC ULCERATIVE COLITIS: PRELIMINARY REPORT. JOSEPH FELSEN, M.D., NEW YORK ... 786

AGRANULOCYTHEMIA: REPORT OF A CASE WITH COMPLETE ANTEMORTEM AND POSTMORTEM RECORDS. C. VICTOR RICHARDS, M.D., BALTIMORE 793

THE DEXTROSE LEVEL OF THE ARTERIAL AND VENOUS BLOOD IN ARTHRITIS. ROBERT M. STECHER, M.D., AND HAROLD J. JEGHERS, B.S., CLEVELAND 801

DETERMINATION OF PLASMA VOLUME:

I. THE DYE METHOD. SAMUEL GRAFF, B.S., AND H. T. CLARKE, D.Sc., NEW YORK 808

II. THE RATE OF DYE MIXING. S. GRAFF, B.S.; D. A. D'ESOPO, M.D., AND A. J. B. TILLMAN, M.D., NEW YORK. 821

BLOOD AMYLASE IN RELATION TO DISEASE OF THE PANCREAS: FURTHER OBSERVATIONS. ROBERT ELMAN, M.D., ST. LOUIS.. 828

I. GOLDSTEIN'S HEREDOFAMILIAL ANGIOMATOSIS WITH RECURRING FAMILIAL HEMORRHAGES (RENDU-OSLER-WEBER'S DISEASE). HYMAN I. GOLDSTEIN, M.D., CAMDEN, N. J. 836

ISOLATED CONGENITAL DEXTROCARDIA: REPORT OF TWO CASES WITH UNUSUAL ELECTROCARDIOGRAPHIC FINDINGS; ANATOMIC, CLINICAL, ROENTGENOLOGIC AND ELECTROCARDIOGRAPHIC STUDIES OF THE CASES REPORTED IN THE LITERATURE (CONCLUDED). S. S. LICHTMAN, M.D., NEW YORK 866

BOOK REVIEWS 904

Medical Libl

99 DEC 3 - 1931

VOLUME 48 IN TWO PARTS—PART II NUMBER 5

ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Cambridge, Mass. WARFIELD T. LONGCOPE, Baltimore

J. H. MEANS, Boston WALTER W. PALMER, New York City

W. S. THAYER, Baltimore

NOVEMBER, 1931

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized June 14, 1918.

Copyright, 1931, by the American Medical Association

Archives of Internal Medicine

VOLUME 48 NOVEMBER, 1931—IN TWO PARTS—PART II NUMBER 5

THE INFLUENCE OF SOLAR RAYS ON METABOLISM

WITH SPECIAL REFERENCE TO SULPHUR AND TO PELLAGRA IN SOUTHERN UNITED STATES

JAMES H. SMITH, M.D.
RICHMOND, VA.

THE INFLUENCE OF SOLAR RAYS ON METABOLISM

WITH SPECIAL REFERENCE TO SULPHUR AND TO PELLAGRA IN SOUTHERN UNITED STATES *

JAMES H. SMITH, M.D.
RICHMOND, VA.

CONTENTS

Introduction
The Effects of Solar and Ultraviolet Rays on Metabolism
The Influence of Radiant Energy and Latitude on Carbohydrate Metabolism
The Present Status of Water-Soluble Vitamin B
Sulphur Metabolism and the Relation of Cystine to Solar Irradiation
Superficial and Remote Effects of Exposure to Radiant Energy
The Theory of a Deficiency of Food as the Cause of Pellagra
Metabolism in Pellagra
Goldberger and Wheeler's Experimental Pellagra in White Male Convicts (in Mississippi, 1920)
Experimental Black Tongue of Dogs and Its Relation to Pellagra
Comparative Data on Pellagra Among Prisoners of War in Egypt
Koch and Voegtlin's Experiments with a Restricted Vegetable Diet in Monkeys
Creatinuria and the Age and Sex Incidence of Pellagra
Geographic Distribution of Pellagra in Relation to Isothermal Lines
Certain Features of the Physics of Solar Radiation
The Influence of Season and Latitude on Metabolism
The Far North
The Tropics
Latitude of Boston and Chicago (42°N.)
Latitude of the Southern United States
Definition of Cloudiness
Accustomed Radiant Energy and Deviation Therefrom
The Seasonal Incidence of Pellagra in Nine Southern States, from 1925 to 1929, Inclusive, in Relation to Solar Radiation
Variations in the Annual Incidence of Pellagra Within the Pellagra Belt
Humidity
Delayed Incidence or Momentum
Areas with a Relatively High Prevalence of Pellagra
The Incidence of Pellagra in Workers in Cotton-Mills
Summary
Conclusions
Bibliography

INTRODUCTION

That there are biologic effects due to radiant energy is not open to question, and that some of these are related to pellagra seems probable.

* Submitted for publication, Dec. 15, 1930.

* From the Medical Department, McGuire Clinic and St. Luke's Hospital.

In epidemic or endemic disease, the experimental laboratory studies so necessary for scientific proof can rarely be undertaken before a fairly complete survey of outstanding epidemiologic features has been made. With regard to pellagra, it is believed that climatic factors, while often referred to, have not received the consideration required for an understanding of the disease. The significance of established factors in the etiology of any disease is not depreciated and may be enhanced by recognition of other significant factors. It is easy to imagine such a result in connection with pellagra when the etiology of rickets is considered, with its interrelated influence of calcium and phosphorus imbalance and deficiency in vitamin D and in ultraviolet rays. In this connection there is recognizable a significance in the condition of the patient in relation to lack of exposure to ultraviolet rays similar to the relation between the resistance of the patient and the virulence of the infection. One factor may be present in a degree of intensity less than the average for the development of the disease, and the disease may still develop because of a greater than average intensity of another factor. The same considerations possibly are applicable to pellagra.

Certain observations bearing on the influence of solar rays in metabolism and in pellagra will be presented, but the only support brought from experimental investigations is taken from the work of others. The data are far from complete and are not always in agreement. The available literature has been reviewed only in part. In general, the study is intended as a basis for further experimental work and as a basis for contemporary observation as suggested by analysis of past events. However, under controlled experimentation and observation with a limited number of subjects, there would remain the possibility that the sampling or selection of subjects failed to take into account some undetermined factor of individual metabolism present in some but not in others of the general population and conditioning the end-result. Such an explanation may account for the fact that a condition considered to be pellagra developed in only six of Goldberger and Wheeler's experimental subjects.

The more significant climatic factors are temperature, humidity, movement of air (wind) and sunlight. Various studies have been undertaken to determine their exact influence on both plant and animal life, including that of man. For example, Tsi-Tung Li [102] calculated partial correlation coefficients for the influence of these factors on the suction force of sap in certain plants, and he gave a coefficient of 163 for the temperature of air, 445 for the intensity of light and 469 for the relative humidity. In the human subject, when the relative humidity is 100 per cent, the minimum metabolism occurs when the temperature of

the air is from 75 to 80 F.[44] These factors will be referred to again, and the effect of ultraviolet irradiation on metabolism will be considered in detail.

On reaching the earth's surface, solar radiation is affected by several factors, including latitude and season. With regard to seasonal variations in biologic phenomena, many instances are matters of common knowledge and many others are well established through special investigation and observation. Rarely is it possible to assign distinct and independent significance to a single climatic factor, and what influence any factor has may be mediated through any one or more of several factors, such as vegetation, the intake of vegetables and mineral and animal food, bacterial or parasitic invasion, or the transmission of disease through an intermediate host, such as the mosquito.

North of the equator (and all references are to the northern hemisphere unless otherwise stated), the summer and winter seasons present the opposite phenomena of maturing and decaying vegetation. In summer, the intake of protein is decreased, and in the winter it is increased. In summer, the iodine content of water and salt is decreased, and the resistance of white mice to nitrile is decreased. In the latitudes from which these data are reported, the iodine content of the thyroid gland is lowest in March, and about the same season the development of goiter is highest. Following the winter months, rickets also reaches its highest seasonal incidence, along with its observed disturbance of calcium-phosphorus metabolism. The list could be extended. The seasonal variations of pellagra will be reserved for further discussion.

As introductory and suggestive of certain of the ideas to be developed, attention is directed to certain studies of Paramecia and of the lens of the eye.

Paramecia were subjected to ultraviolet rays that had previously passed through solutions of cystine $\left\{\left\{CH_2S\text{–}CH\begin{matrix}NH_2\\COOH\end{matrix}\right\}_2\right.$ in sodium hydroxide.[40] The time of exposure required to produce fatal results was 1,200 seconds, if the ultraviolet rays first passed through the cystine solution, as compared with 150 seconds in the controls. From this it is argued that susceptibility of protoplasm to ultraviolet radiation is conditioned by the selective absorption of the toxic rays by cystine—and certain aromatic amino-acids. Ward,[114] in his studies of the absorption spectra of amino-acids, found that cystine was the only amino-acid that had any marked absorption in the region of solar ultraviolet rays. It would appear that the relatively high concentration of cystine in wool and hair is of physiologic importance in the protection of the organism against the harmful effects of prolonged exposure to sunlight.[39] The eyelashes

may be endowed with a function more delicate than that of protecting the eye against the entrance of foreign bodies.

Light of wave length 760 to 380 mμ. (the lower limit being variable and depending to some extent on the age of the individual) penetrates to the retina and is perceived as visible light. Light from 380 to 295 mμ. is absorbed by the lens and causes it to fluoresce. Light of wave length shorter than 295 mμ. is absorbed by the cornea and conjunctiva, producing a severe ophthalmia.[15]

Although it is possible that heat may be a contributing cause in glass-blowers' cataract, there is no evidence of injury to the eye by heat except in eclipse blindness, which is probably due to heat coagulation of the retina.

Light from 295 to 385 mμ. although absorbed by the lens, produces no ill effect as a rule. Most proteins are coagulated by the ultraviolet light which they absorb, but the lens protein seems to be resistant in this respect, at any rate for the wave lengths 295 to 385 mμ. The light absorbed by the lens causes a strong fluorescence in it, and Burge [11] suggests that the fluorescence constitutes a protective reaction, but the nature of the protection is not clear. It may be mentioned, as a matter of interest, that in some nocturnal animals (rats, mice) the lens does not fluoresce to waves of this length. Burge has shown by a series of ingenious experiments that, in the presence of certain salts, lens proteins coagulate with light longer than 300 mμ., and he supposes that a combination of nutritive disturbances and strong light may account for the development of cataract. With this possible exception, however, the light absorbed by the lens is harmless.

Laurens stated [57] that there are two rather divergent and apparently conflicting ideas as to the influence of radiant energy as a causative element in the production of cataract. Both of them may be found to be compatible, for either the infra-red or the ultraviolet radiation may superinduce cataract under certain physiologic conditions of which nothing is as yet known (Sheard).

Gradle [34] has recently presented statistics as to the age of patients in various parts of the northern hemisphere operated on for senile cataract.

Table 1 gives the statistics and shows the geographic location of the surgeon as given by Gradle. A notation of the latitudinal location is also included. There is a noticeable tendency for the patient with cataract to be operated on earlier in the regions nearer the equator. Wright, in order to furnish a comparison of an equal number of Indian cases with the 4,230 Caucasian cases, carried his study far enough to serve this purpose, and he found that the Indian percentages remained practically what they were when worked on the first 500 tabulated. At Memphis, the next most southerly clinic quoted, the patients were not so young as the Indian patients, but were somewhat younger than the Caucasian group as a whole, as represented by the American and European cities farther north and including Memphis. In discussing the comparison between the Caucasian and the Indian people, Elschnig, of Prague, con-

sidered that it furnished good proof for the words that Hirschberg wrote in 1898 in the "History of Ophthalmology": "Under the glowing sun of India, cataract ripens fully twenty years earlier than with us."

Among the tissues of the body which give a strongly positive nitroprusside reaction, is the lens of the eye.[59] Goldschmidt [33] has studied the cysteine content of the lens of cattle at various ages, as determined by the ability of the tissue to form hydrogen sulphide from elementary sulphur according to the general reaction:

$$\begin{matrix} R-SH \\ R-SH \end{matrix} + S = \begin{matrix} R-S \\ | \\ R-S \end{matrix} + H_2S$$

TABLE 1.—*Age of Patients Operated on for Senile Cataract and Geographical Location of the Surgeon, as Reported by Gradle*

			Degrees	Minutes
1	Benedict	Rochester	43	30
2	Derby	Boston	42	30
3	Ellett	Memphis	35	
4	Elschnig	Prague	50	
5	Kalt	Paris	49	
6	Knapp	New York	41	
7	Meller	Vienna	48	
8	Sinclair	Edinburgh	56	
9	van der Hoeve	Leiden	52	
10	Wessely	Munich	48	
11	Wright	Madras	12	
12	Gradle	Chicago	42	

Number	Latitude, Degree	Cases	20-30, per Cent	30-40, per Cent	40-50, per Cent	50-60, per Cent	60-70, per Cent	70-80, per Cent	80+, per Cent
8	56	250	0.8	2.0	4.0	21.8	38.8	28.8	4.0
9	52	100	0.0	0.0	2.0	16.0	39.0	31.0	12.0
4	50	1,000	0.0	0.7	6.6	21.1	41.8	27.2	2.6
5	49	500	1.0	1.6	6.8	18.8	37.6	30.6	3.8
7	48	500	0.0	0.0	3.0	20.2	40.4	33.2	3.2
10	48	509	0.0	0.0	2.9	12.6	36.9	41.7	5.9
1	43	571	0.7	4.0	6.8	21.9	35.0	25.2	6.4
2	42	100	0.0	0.0	6.0	20.0	45.0	28.0	1.0
12	42	100	0.0	0.0	7.0	16.0	39.0	26.0	12.0
6	41	100	0.0	1.0	1.0	24.0	41.0	27.0	6.0
3	35	500	0.6	3.8	9.1	22.0	32.4	27.2	4.6
11	12	500	0.2	4.4	15.8	29.6	41.2	8.4	0.4
Average		4,730	0.21	1.40	5.86	20.28	38.95	27.74	5.56
Caucasian average		4,230	0.23	1.21	5.04	19.51	38.83	29.58	5.60
Indian average		500	0.2	4.4	15.8	29.6	41.2	8.4	0.4

The cysteine content of the lens, as determined by this method, varied little in calves between the ages of 8 days and 1 year, but there was a diminution of the cysteine content of the lens in adult life (1.3386 per cent cysteine in the lens of calves, 0.5820 per cent in the lens of cattle 8 to 17 years of age). No differences could be observed in the total sulphur content of the lens at different ages.

In cataract of the lens, however, the nitroprusside reaction was absent and the lens was unable to reduce elementary sulphur to hydrogen sulphide. If the lens was first treated with sodium sulphite (which reduces cystine to cysteine) the cataract tissue behaves as a normal lens, thus demonstrating that the failure of hydrogen sulphide formation was due, not to a cystine deficiency, but to the inability to form cysteine.

Goldschmidt considers that the amount of cysteine present may determine the oxidative processes of the lens and play an important rôle in the pathology of cataract.*

THE EFFECTS OF SOLAR AND ULTRAVIOLET RAYS ON METABOLISM

In examination of the data with reference to the effects of solar and ultraviolet rays on metabolism discrepancies are noted, due doubtless at times to lack of standards of measurement of the rays and of influences by which they are modified, and to differences in the human and other animal subjects. The usual caution in applying to man the results of animal experimentation is necessary. In particular, with regard to vitamin B, birds and mammals appear to have different requirements, and it is further important to keep in mind a distinction between normal subjects on normal diets and abnormal subjects on abnormal diets. Attention will be directed more especially to the facts of protein metabolism as represented by nitrogen and sulphur, and to the basal metabolism.

Weiner (quoted by Laurens [57]) carried out two long experiments on normal men, giving them irradiations from a carbon arc that did not have an ultraviolet ray shorter than 290 mm., being comparable, therefore, to solar rays. During irradiation, the excretion of nitrogen was diminished, while after it there was a shift to a nitrogen equilibrium on a higher level than that present during the preliminary period, and the negative balance became positive. Koenigsfeld, using a quartz mercury lamp, reported an opposite initial disturbance, but the same end-result of an increased retention of nitrogen. In Weiner's observations, the excretion of sulphur was not affected. Koenigsfeld found the elimination of sulphate increased. The emphasis here possibly belongs on the fact that in normal subjects the nitrogen equilibrium was reestablished on a higher level than before, and there was a retention of nitrogen.

Eichelberger's report is of especial interest in view of the observed low excretion of creatinine in pellagra. Eichelberger found that the excretion of creatinine is increased during an hour of irradiation (carbon arc or sunlight) and then decreased for several hours, after which it returns to the preliminary level. Possibly the emphasis here belongs on the secondary increase as the normal reaction. Heat was shown not to be a causative factor.

---

* This is Hammett's conception of the conditions in sluggish ulcers of the skin (Hammett, reference 38). If further investigation should show that a similar disturbance of sulphur metabolism occurs in the tissues of the pellagrin, then by a slight stretch of the imagination, cataract could be looked on as pellagra of the lens, and the glass-blowers' cataract would represent the "dermal type," while the senile, and perhaps the diabetic, cataract would represent the "systemic type."

Laurens stated, "we might expect that transition from darkness to roomlight would produce results somewhat similar to irradiation with a strong source of radiant energy, but it is somewhat surprising to find that a change from light to darkness shows similar if less pronounced effects." The emphasis here seems clearly to belong on the influence of shifting conditions of ultraviolet exposure and introduces the principle of acclimation, the possible significance of which in pellagra appears largely to have been overlooked. In a shift either way and following irradiation, there is a stimulation of endogenous nitrogen metabolism resulting in a decrease in the balance. These experiments, as Laurens said, are indicative of a relationship between a positive or a negative variation in the amount of radiant energy acting on the organism and an initial disturbance of metabolism.

Mayerson, Gunther and Laurens found that under the shifting influence of darkness to light, and vice versa, normal adult dogs on an adequate diet showed an initial effect of increased nitrogen metabolism, as shown by an increased excretion of urea and creatinine, which usually decreased to normal by the end of the period.

From these and similar reports, the general conclusion seems to be warranted that moderate irradiation of normal subjects does not result in permanent change in the metabolism of proteins, and that for a time there is a shift to a nitrogen equilibrium on a higher level.

THE INFLUENCE OF RADIANT ENERGY AND LATITUDE ON CARBOHYDRATE METABOLISM

The effect of radiant energy on carbohydrate metabolism has also received some attention from investigators. Burge and Wickwire [12] found that Paramecium caudatum utilizes all of the simple sugars: dextrose, levulose and galactose. Dextrose and levulose are used more rapidly than galactose, as is the case with the higher animals.

Ultraviolet radiation decreases the utilization of the sugars by these animal cells, without at the same time killing or injuring the cells.

Ultraviolet radiation destroys insulin.

The addition of insulin to the liquid containing the organisms prevents the decrease in sugar metabolism by the ultraviolet rays. The decrease in the utilization of sugar brought about by ultraviolet radiation is attributed to the destruction of the insulin in the cells by irradiation.

Cori and Cori [17] reported that during the summer months, rats excrete an average of 6.2 mg. of total acetone bodies per hundred grams of body weight per twenty-four hours, from the twenty-fourth to the forty-eighth hour of fasting. During the winter months, the excretion of acetone bodies was only 1.9 mg. The influence of temperature was excluded. The ketosis was associated with a reduced capacity of the tissues to oxidize dextrose.

Sundstroem [98] concluded that the level of the blood sugar in the tropics not only never reached an excessive height, but rather tends to occupy low levels. As a rule, descendants exhibit lower levels than immigrants. Mills [69] found that the death rate from diabetes increases as the distance from the equator becomes greater. Whether or not the observations of Sundstroem and of Mills will in any degree find a basis in those of Burge and Wickwire and of Cori and Cori is problematic. It appears rather that they tend to conflict. However, concerning the unicellular organisms studied by Burge and Wickwire, account should be taken of the possible influence in man of specialized tissue, such as the suprarenal glands, and the observations of Cori and Cori were in connection with rats during fasting rather than with the organism of man, on a diet normal for the environment.

THE PRESENT STATUS OF WATER-SOLUBLE VITAMIN B

A disturbance of nitrogen metabolism in pellagra, as evidenced by a study of the partition of nitrogen in the urine, has been described by several investigators, particularly by Sullivan and his co-workers. In contrast to the effects of ultraviolet irradiation under normal conditions is the statement of Eckstein (quoted by Laurens [57]), that rats on a vitamin-free diet remain alive in comparatively good condition although their development is slow. If they are given irradiation, they die in from twelve to thirty-one days, "the disturbed metabolism being able to stand the additional strain put upon it by radiation."

Extensive and prolonged experimental investigation has failed to yield an answer as to the chemical nature of the different factors involved in vitamin B, and the futility of attempting to deduce from observation the identity of the pellagra-preventive factor is too obvious to need comment. The complexity of the problem as it stands at present is clearly outlined in Kruse and McCollum's [54] recent review, from which the following abstracts were taken.

There is a difference of opinion regarding the effect of ultraviolet irradiation on the antineuritic principle. Working independently, Zilva and Spinka agreed that the exposure of yeast to ultraviolet rays for twenty minutes at a distance of 6 inches (15.24 cm.) did not have any effect on the activity of its vitamins. R. R. Williams, however, asserted that the antineuritic factor in an aqueous yeast extract was completely destroyed by irradiation for a few hours. By spectrographic technic, Damianovich made the highly interesting observation that an active extract of yeast, although practically colorless, showed a characteristic absorption band between 2,478 and 2,600 angstrom units, which seemed to correspond to that of pyrimidine compounds.

There are unknown substances that accelerate the growth of yeast. The generic name "bios" is given to this class of substances. Bios is not necessary for the growth of yeast, but makes it grow more rapidly.

Koch and Sugata [52] reported that the studies of Swoboda in their laboratory indicated that cystine stimulated the growth of yeast when added to certain mediums. This suggested a more intensive study on the actual utilization of various forms of sulphur in the growth of yeast. The authors reported this study in detail, finding that cystine stimulates the growth of yeast slightly in concentrations of from 1 to 4 mg. per 125 cc. medium, but retards it in higher concentrations. The stimulation is less than that from certain other forms of sulphur.

Kruse and McCollum, in summarizing the relation of the pellagra-preventive factor to water-soluble B, said that Goldberger and his co-workers found: 1. The antineuritic factor (vitamin B *sensu stricto*) is distinct from the pellagra-preventive factor and does not in itself suffice for the growth of rats. 2. If, as some investigators have suggested, the term "water-soluble B" includes, in addition to the antineuritic factor, a so-called growth-promoting essential (possibly identical with Wildier's bios), this, like the antineuritic factor, is either inactivated by autoclaving or does not suffice by itself for the growth of the rat. 3. The pellagra-preventive factor or some associated pellagra-preventive factor (possibly the so-called growth-promoting factor) distinct from the antineuritic vitamin, though not sufficing in itself for the growth of the rat, is, in combination with the antineuritic vitamin, essential for growth in rats. Thus, Goldberger and his associates confirmed Hendrick and Smith's statement that there are two factors in water-soluble B which are necessary for the rat.

Lecoq has provisionally postulated the presence of four different vitamins of the B type in yeast: the antineuritic vitamin of Funk, the nutritive vitamin of Randoin and Lecoq, the antipellagrous vitamin of Goldberger and his associates and the growth-promoting vitamin of yeast of Funk and Dubin.

Kruse and McCollum concluded that where there had been one substance awaiting isolation, no one knows how many there are now. At present there is no clarity in regard to the relation of the various essential components described by investigators; for instance, whether all of the thermostabile factors are identical (the pellagra-preventive vitamin is thermostabile), or whether the alkali-stabile factor is the same as a thermostabile factor. Moreover, Funk's contention that bios is related to vitamin B as an essential factor for the growth in animals must not be forgotten. This contingency presents difficulties when it is remembered that bios has been separated into three fractions.

Goldberger and Tanner thought that a deficiency of amino-acids is probably the primary etiologic factor in pellagra, although in 1920 Goldberger and Wheeler had taken somewhat more latitude in their conclusions:

> In relation to the production of pellagra, the dietary factors to be considered as probably essential are: (1) an amino acid deficiency, (2) faulty mineral supply or constitution and perhaps (3) an as yet unknown (vitamin?) factor. As to which or what combination, or combinations, of these constitutes the specific pellagra-producing dietary defect or defects remains to be determined.

Various writers have taken exception to these conclusions. For example, Mitchell,[70] in 1924, thought that while it is clearly established that dietary error or errors of some description are primarily responsible for pellagra and that the presence of certain amounts of protein-rich animal foods, particularly milk and meat in the diet, is an effective preventive against this disease, the disease has not been definitely traced to deficiency of protein or amino-acid, "even though the arguments of the proponents of this deficiency theory are granted *in toto*." Enright[25] concluded: "I do not mean to suggest that a food deficiency can be quite excluded, but from the facts before us it can hardly be considered as of paramount importance." Bigland[6] and Wilson[119] disagreed with Enright.

SULPHUR METABOLISM AND THE RELATION OF CYSTINE TO SOLAR IRRADIATION

In 1919 and 1920, Sullivan and his co-workers suggested that in pellagra the sulphur metabolism is abnormal. Cammuri, in 1910, and Myers and Fine, in 1913, reported abnormalities of sulphur metabolism in pellagra.[46a] With a view to further consideration of this point, certain data with regard to cystine metabolism and a specific relation of cystine metabolism to solar irradiation will be reviewed.

The demands of the organism for sulphur are supplied largely by cystine.[53] It is necessary not only to the growth * but to the maintenance of animals (Lewis,[59] pp. 401, 418 and 447). Its function in the organism appears to include an important bearing on the oxidation of tissue through the reversible cystine⇆cysteine reaction (Dakin[19] and Lewis[59]) and a detoxifying influence on certain compounds, at least one of which, cyanogen, is a product of protein metabolism.[59]

Protein sulphur is present in varying proportions in different foods, as represented by its increased percentage in serum albumin as compared with casein. Under conditions of a low intake of protein, serum

* "It is obvious, however, that some amino acids, such as lysine and cystine, are required in relatively greater amounts for growth than for maintenance" (Mitchell, reference 70).

albumin is more effective in maintaining nitrogenous equilibrium in dogs than is casein. However, when casein is supplemented by cystine, it is as efficient for the maintenance of the nitrogenous equilibrium as is serum albumin.

The tissues generally give a nitroprusside reaction (Lewis [59] and Lewis, McGinty and Root [62]), but in rats on synthetic diets from which cystine was absent, nutritive failure was accompanied by an abnormally weak nitroprusside reaction in the tissues (Lewis,[59] p. 418). Definite proof as to whether the disulphide, cystine, or its reduction product, cysteine, actually exists in the protein molecule is lacking (Lewis,[59] p. 398), though the presence of cysteine is regarded as probable (Lewis,[59] p. 399).

According to Sullivan's investigations,[93] glutathione, a dipeptide,* containing cysteine and glutamic acid, which was isolated by Hopkins (Lewis,[59] p. 415) by extraction from brewers' yeast,† gave neither the cystine nor the cysteine reaction. However, there is little apparent tendency to question the importance of glutathione in oxidative processes through the reversible cystine $\rightleftarrows$ cysteine reaction. Kendall [47] claimed that oxygen and sulphur are important in the promotion of this reaction. Abderhalden (quoted by Laurens [57]) suggested that normally the reaction $R.S\text{-}S.R \leftrightarrows R.SH + HS.R$ is balanced, that in "alimentary dystrophy" (the term applied to the condition of malnutrition resulting from lack of specific substances in the diet, vitamins ‡) in birds fed rice the reaction proceeds in only one direction, $R.SH + HS.R \rightarrow R.S — S.R$, reversal of the reaction is prevented and mercapto groups necessary for the oxidation are not available, and that in cyanide poisoning, the reaction can proceed only in the opposite direction, $R.S — S.R \rightarrow$

* A tripeptide containing cysteine, glutamic acid and glycine (Hopkins and Harris, reference 41a).

† "If the investigation of vitamin B has not yielded the desired results, its indirect effects have not been barren. While engaged in methods for isolating the antineuritic substance, Hopkins gained a discovery of equal magnitude, the separation of glutathione. Somewhat similar fortune befell several Japanese investigators in the finding of new compounds among the constituents of rice. In their search for vitamin B in yeast extract Suzuki, Odaki and Mori obtained crystals which they later identified as adenylthiomethylpentose. From the same source Odaki succeeded in separating a new thio-amino acid and several unknown bases. Funk found nicotinic acid in the vitamin fraction of rice polishings. . . ." (Kruse and McCollum, reference 54).

‡ It would appear that any condition, even though arising at an earlier period, that interferes with intestinal absorption may, under conditions favorable to the development of pellagra, result in an effective lack of the pellagra-preventive food factor. Thus the incidence of hookworm in pellagrins (Kentucky State Board of Health, reference 49, and Shelly, reference 87) or dysentery (Bigland, reference 6, and Enright, reference 25) might predispose to pellagra, and any geographical area may have a factor with a special influence on the etiology of the disease.

R.SH + HS.R, and utilization of the mercapto groups present for oxidation is not possible, since cyanides prevent conversion of the mercapto groups into disulphides. The ultimate result in poisoning caused by cyanide and in alimentary dystrophy is the same, failure of oxidation, but, as stated, the mechanism by which oxidation is prevented is different.

The excretion of urinary neutral sulphur in poisoning caused by potassium cyanide and carbon monoxide is increased.[53]

Following the recognition of a high concentration of sulphydril (— SH) in the living part of the tissue of a tumor [113] and its importance in the nuclear activity of cell division, Hammett [38] concluded that it is specifically essential to the nuclear processes of cell division, and that normally an equilibrium is maintained through the reversible cysteine ⇆ cystine reaction, controlled according to the law of mass action. He consistently obtained a marked intensification of the nitroprusside reaction for sulphydril on injury of the tips of the root, either by crushing or by scratching. Giroud and Bulliard noted an association between the concentration of sulphydril in the skin and keratinization, while Lightbody and Lewis [64] confirmed this principle on dietary grounds. Reimann,[79] quoting Hammett, considered that the essential difference between the nucleus of a cell in mitosis and that of a cell in the resting condition is a rearrangement of the sulphur molecules so that this element appears in the chemical group sulphydril. He stated that "if the sulphydril radical is the stimulus to cell division, the products of the reaction of sulphydril accumulate and stop mitosis by the time the wound is healed." These ideas led to the use of thiocresol to stimulate the healing of wounds.

The action of radiation on the healing of wounds is due, in great measure, to the influence on cell division.[57]

The sulphur of cystine is readily oxidized in the body, as is also the sulphur of dipeptides containing cystine.[59] The excretion of sulphur is largely in the oxidized form of sulphates. If complete deamination is prevented, as by the feeding of phenyluraminocystine [62] or the injection of dibenzoylcystine,[63] oxidation is not complete and a cysteine derivative of cystine is excreted in the urine. When cystine was injected into dogs on a diet low in protein and brombenzene was fed, an abundant synthesis of bromphenyl-mercapturic acid occurred. Cystinuria represents an "error of metabolism" which is but little understood.[59]

The production of thiocyanates in the urine, as well as in the saliva, is increased after the ingestion of nitriles and certain amino-acids, and their appearance is usually considered to be due to a defensive process whereby the toxic cyanogen radicals are converted into the less toxic sulphur cyanogen compounds (Lewis,[59] p. 406).

After a prolonged fast followed by the ingestion of large amounts of meat, there is a distinct lag in the excretion of sulphur (Lewis,[59] p. 410), indicating either a retention of a sulphur-rich protein in the period of recovery from inanition or a much more striking lag in the elimination of sulphur than is usually observed (Wilson [118] and Schmidt and Clark [85]). Fay and Mendel stated that "the great increase in the value of the ratios during the earlier days of feeding adequate diet after starvation can be interpreted in only one way—specific retention of sulphur."

When fed to rabbits in large doses, cystine is found to be toxic.[60] Wilder [117] referred to the injurious effects of cystine on the liver and its possible etiologic influence in pernicious anemia.

The high content of the epithelial protective tissue in sulphur and cystine, a content greater than that of any other tissue of pure protein, suggests that the cystine may have a specific function in this tissue.[59] The protective action of cystine solutions when Paramecia are exposed to ultraviolet radiation and the finding of Ward that cystine was the only amino-acid that had any marked absorption for ultraviolet rays have been referred to. Ward called attention to the fact that the curious custom of the Arabs of wearing heavy woolen clothing may have a strong justification in the protective effect of the cystine in the wool.[44]

Lightbody and Lewis [64] discussed the relation of protein and sulphur content of the diet to the growth of hair in the white rat. Remington [80] discussed the cystine yield and total sulphur in the hairs of various animals.

Sundstroem [98] noted that a return from the tropics to a cooler climate resulted in a considerable stimulation of the growth of hair, "which growth then proceeded with seasonally determined cycles, exhibiting a maximum in June and a minimum in December." This report would seem possibly to be related to Laurens' finding of an effect of deviation from exposure to the accustomed radiant energy.

Sundstroem also stated that the reports on excretion of neutral sulphur in the tropics are conflicting and do not prove an augmented catabolism of body protein in tropical man.

In general, Lewis [59] held that experiments which indicate a special relation of cystine to the growth of epidermal tissues rich in sulphur (and cystine)—hair and wool—(Abderhalden,[1] Blaschko,[7] Fuhs,[28] Zuntz [121] and Zuntz [122]) are interesting, but further work under more carefully controlled conditions is necessary before the specific rôle of cystine in the growth of hair can be accepted without qualification.

The circumstances of excretion of creatine in the urine have been investigated rather extensively, but its significance has never been definitely determined. In discussing Harding and Young's suggestion that

cystine is a precursor of creatine in the growing dog through the intermediate stages of taurine and amino-ethyl alcohol followed by methylation, combination with urea and oxidation, Lewis [59] explained:

> In view of the fact that creatine is determined as creatinine after dehydration in the presence of acids, and that many of the reactions by which creatinine is usually identified are also given by cysteine and mercapto derivatives, it seems possible that the variations of the creatine content of the urine observed may have been due to the presence in the urine of mercapto or other derivatives of cystine.

An increased excretion of creatine by the pig has been observed after the ingestion of cystine.[35] The increases, however, were considered to be due to acidosis resulting from the oxidation of the cystine sulphur to sulphuric acid. Further observations on the occurrence of creatinuria and its possible significance will be referred to later.

Hopkins isolated glutathione from yeast, muscle and hepatic tissue.[39] Dakin stated: [19]

> The concentration of glutathione in the tissues is very low, but its distribution is extremely wide. The blood proteins appear to contain vanishingly small amounts or possibly none, and this observation agrees with the growing conviction that scarcely any oxidation of moment occurs in this medium. Yeast furnishes useful material for the preparation of glutathione though animal organs may serve equally as well.

Reference has been made of the influence of sulphur as "bios" in the growth of yeast.

Fay and Mendel,[27] in a study of nitrogen and sulphur metabolism in the dog, selected the proteins entering into the different rations on the basis of their differing sulphur content: casein low in sulphur content, "meat residue," which has a slightly higher percentage of sulphur, and egg albumin, which is comparatively rich in sulphur. Along with casein, beans of the genus Phaseolus are rated low in cystine content by Mitchell.[70] Cohn [16] stated that most known proteins are poor in tryptophan and cystine; nevertheless, their necessity for growth in the young, and for maintenance of nitrogen equilibrium in the adult animal is fully attested. In view of the poverty in cystine characterizing proteins generally it is of interest to note its occurrence in the foods that Goldberger and his associates advocated as preventive of pellagra and to note that these foods contain cystine (or sulphur) in proportions comparable to the value for the prevention of the disease assigned them by this author.

SUPERFICIAL AND REMOTE EFFECTS OF EXPOSURE TO RADIANT ENERGY

A certain protective value of pigment against the effects of exposure to solar rays, as well as the necessity to regulate the degree of exposure in order to avoid definitely pathologic effects, is a matter

of common knowledge. On the other hand, it is equally obvious that pigmentation does not protect against pellagra. Only a superficial view of the matter, however, would lead to the inference that solar rays are without influence in the causation of pellagra.

It has been suggested that the dermatitis of pellagra may represent a local and superficial effect of radiation unrelated to the essential nature of the disease as a disturbance of metabolism. A variety of considerations tend to contradict this view. If it were true, pigmentation would protect against pellagra as it does against sunburn, but that it does not is shown by the relative incidence of the disease in the white and colored races in the southern United States. Again, the mortality from pellagra is higher in the white than in the Negro race. If the cutaneous lesions of pellagra represented a relatively nonessential feature of the disease and were more or less incidental to exposure to the sun, the lightly pigmented white race would probably be more susceptible to solar influence than the colored race, would more readily exhibit superficial and nonessential lesions of the skin and would be more prone to a mild and nonfatal form of the disease, and the mortality from pellagra occurring in the white race would probably be lower than that from pellagra in the Negro; however, such is not the case. The sore mouth, the diarrhea and the symptoms referable to the nervous system constitute a triad that is in itself conspicuous and a rather definite manifestation of the disease. If this triad were a matter of common occurrence independent of dermatitis, the skepticism of the most experienced clinicians with regard to "pellagra sine pellagra" would hardly exist. It is manifest that solar and ultraviolet rays have effects on metabolism not comprehended in the mere production of pigment, and that irradiation is productive of pellagrous effects more profound than dermatitis is suggested by clinical observations such as those of Enright [25] and the notations of Koch and Voegtlin [53] in their experiments on monkeys. These studies will be referred to again.

Laurens suggested that the remote effects of irradiation may be largely thermic, associated with the fact that pigmented skin holds more heat and may facilitate thermotherapy (Laurens,[57] p. 14). Freund showed that the epidermis from blisters absorbed everything shorter than 325 mμ., while hardened scales of skin absorbed everything shorter than 344 mμ. when yellow and shorter than 329 mμ. when colorless (Laurens,[57] p. 10).

The process of pigmentation is essentially the deposit of melanin in the basal cells of the epidermis (Adami [2] and Clark [15]). Acquired pigment is extracellular, in contrast to its normal intracellular position as in the skin of Negroes.[57] Melanin and keratin have a high sulphur

content (Koch and Voegtlin [53] and Lewis [59]). Melanin is nonfluorescent, while epidermal keratin, white hair and sebum are fluorescent.[37] Photodynamic action, however, is not proportional to fluorescence. Fluorescence is the usual accompaniment, but not the fundamental cause, of the sensitization in photodynamic action, "a sort of outward and visible sign, so to speak, of an inner activity in response to light" (Clark,[15] p. 288). Ultraviolet irradiation is not the only influence that determines the color of the skin, other climatic factors, perhaps, being equally or more important.[57] Goodale found that the natural covering of chicks is not penetrated by the effective wavelengths, and that the main receptor is the small amount of naked skin about the bird's head.

Hausser and Vahle (quoted by Laurens [57]) showed that the efficient wavelengths for both erythema and the formation of pigment are near 300 mμ., and that the two conditions are intimately connected, pigmentation following the action of particular wavelengths only when an erythema has been produced, although a slight erythema may occur without the subsequent formation of pigment.

Laurens [57] described the histology of irradiated skin as follows:

> The vessels become dilated with infiltration of the epithelial layer and an abnormal thickening and darkening. Following intense irradiation there is serofibrinous or cell-rich, often hemorrhagic, exudation. If the irradiation is severe enough, the collagenous tissue becomes swollen and homogeneous, the epithelium swollen and loosened, infiltrated and blistered, the loss of continuity occurring at the boundary between the granular and horny layers. If the irradiation is quite intense thrombi form in the vessels of the cutis. . . . The hair follicles and sebaceous glands break down and are regenerated from the epithelium.

For convenience, the cutaneous pathologic changes of pellagra as described by the Illinois Commission [46] are given here. In a large number of sections studied, the general picture was that of an angioneurotic process and resembled to a marked extent that seen in multiform erythema. The most marked change was seen in the superficial part of the corium, almost all of the infiltration occurring in the pars papillaris. The specific observations were as follows: Under low power magnification the stratum corneum appeared thickened; the stratum granulosum and rete were practically normal. The upper portion of the corium showed inflammatory reaction, and the connective tissue appeared edematous. Under high power, the hyperkeratosis was seen to be well marked. Here and there, areas of parakeratosis were present, as evidenced by the presence of nuclei extending to the upper layer of the stratum corneum. Many pigment granules were present. The rete was practically normal, except in places where its integrity was interfered with by infiltrating cells. Cellular infiltration was quite marked in the papillary layer, particularly

in the region of the blood vessels. Collagen and elastin were present, the former showing edematous changes. The deeper parts of the corium were comparatively normal. Elastin was absent from parts of the papillary layer.

Lewis and Zotterman have recently shown that the reactions to injury of the cutaneous vessels by ultraviolet radiation, as by freezing, burning, etc., are due to the production of vasodilator substances in the skin which diffuse into the surrounding skin and are conducted away by lymph channels.

In the "white" race, the color of the skin ranges from light bluish white or pinkish, as in the Nordic blonde or red-haired, to all shades of tan (many Mediterraneans) or brown (some Arabs, Egyptians, Abyssinians, etc.) to almost black (some Abyssinians and Hindus). "In general, the pigmentation of the races of the world varies according to the intensity of sunlight, . . . for pigmentation appears to be primarily a protection against ultraviolet light" (Hrdlička [42] and Huntington [44]).

In this connection it may be noted that the bodily distribution of pigment in the skin presents certain anomalies not in accordance with the principle of exposure to light or other climatic influences. In the nonhairy human subject, the nipples, axillae and genitals are usually areas of relatively high pigmentation. Anatomically, if not by habit of clothing, these areas are relatively protected from the operations of climatic factors. In the dog, the hairless scrotum may or may not show an excess of pigmentation. With regard to the axillae and scrotal area of the human subject, it would appear that the loss of heat by irradiation is minimized by the anatomic arrangement, whereas by evaporation it is increased. A similar function appears to be exercised by the tongue of the dog. Sundstroem [98] noted that in mice exposed to "artificial tropics" the tails and the ears became longer and the scrota pendulous and hairless. In more recent work on rats, the rôle of an enlarged scrotum, for instance, in assisting in the loss of heat, has been proved almost beyond doubt. These considerations may have some bearing on the scrotal lesions of Goldberger's experimentally produced pellagra and experimentally produced black tongue. A tendency to development of hair is also noted in the region of these pigmented areas at the time of development of the secondary sex characteristics.

It would seem that the lesions of pellagra may appear on parts previously or habitually exposed, individually or phylogenetically, and therefore pigmented, rather than necessarily on parts exposed after a deficiency in food is instituted.

Any protective influence exercised by pigment is apparently not by virtue of impenetrability to light. Kinney observed the relative pene-

tration of light through three hands from a blonde, a brunette and a Negro, respectively, which calibrated to exactly the same thickness. In both fluoroscopic and photographic tests, the penetration was greatest in the Negro, less in the brunette and least in the blonde.[92]

It is not clear just how effects distant from the area of the skin irradiated are brought about. A mediation through the nervous system may be involved. The therapeutic results obtained in deep-seated tuberculous lesions are familiar. Lewis and Zotterman's ideas with reference to the conduction of vasodilator substances by the lymph channels have been referred to. Burchardi demonstrated that irradiation no longer influenced the blood picture after pigmentation, and Rothman showed the same factor for the depression of blood pressure and blood sugar and an increase in serum calcium.[57] Buckwheat sensitizes cattle to the effects of light, but pigmentation reduces the susceptibility. Hematoporphyrin is an active sensitizer to light.[15] Black and gray mice apparently cannot be sensitized to light by hematoporphyrin, while white mice can be.[57] Metallic compounds, especially sulphur and halogen compounds, show photo-electric action and are extremely phosphorescent.[15]

Hess, Weinstock and Helman suggested that the beneficial action of irradiating an animal is produced through the activation of cholesterol in the skin, from which it is absorbed and circulated in the blood stream.[57] Sheppard's [88] active substance in gelatins for photographic purposes (thiocyanate) went down with a condensate chiefly cholesterol, but the cholesterol was not active, and it was concluded that the active substance was dissolved only in the sterols and not chemically combined.

Laurens [57] stated that the only reasonable conclusion is that, following ultraviolet irradiation, some photochemical substance that is formed in the skin is carried by the blood stream "to these various organs, there bringing about the observed changes." Hess and his co-workers [41] said that it should be remembered that in the course of activating ergosterol by means of ultraviolet radiations a series of products is formed, the sterol passes through various chemical phases, and the final product is a mixture rather than a photochemical entity.

In a "seasonally" conducted series, proof was obtained for an antagonistic behavior of the lecithin and cholesterol curves, high levels for the former coinciding with low levels for the latter, and conversely.[98]

Clark [15] elaborated a theory as follows: Light shorter than 300 mμ. acts on the living cell by ionizing its photo-electric constituents and thereby leading to photochemical action. Light longer than 300 mμ. acts in the same way in the presence of sensitizers which so affect the surface conditions of these constituents that their photo-electric thresh-

old is shifted into the visible, and they therefore become ionized with resulting chemical action when illuminated by visible or near ultraviolet energy.

Sheppard,[58] in an investigation of the "sensitivity substance" in the gel from animal hides for the manufacture of photographic films, found that it lay in the doubly bonded sulphur as represented by allyl-isothiocyanate (mustard oil), which is believed to be derived from the food previously utilized by the animal, and that for a given emulsion and given conditions the sensitizing effect of the active body reached a maximum for a certain quantity (in the order of 1:300,000) and then decreased as the amount of the active material was increased further.

When mustard oil was added to the system of the Kottmann reaction (unpublished experiments, J. H. S., 1928), it was found to alter the speed of the reaction in human serums and commercial gelatins; however, the results were not consistent. The extreme nicety of control of a variety of factors influencing the sensitivity of photographic emulsions is brought out by Davis and Withers.[20]

The considerations advanced have been chiefly in connection with normal subjects. A difference between "sick skin" and normal skin is postulated by many writers. Bovie (quoted by Laurens [57]) emphasized that it is the instability of the physiologic mechanism rather than the wavelength that determines the nature of the physiologic effect produced. Clark [15] traced the analogy between the photographic process and the physiologic action of light, stating that there is considerable evidence to show that diseased tissue is more susceptible to radiations than normal tissue. "To push the photographic analogy further, we may assume that normal tissue acts like a slow plate and diseased tissue like a fast one." Or, as Laurens [57] stated: "The sick organism is a much more delicate mechanism than the well, diseased tissue being more susceptible to radiation than normal, while the animal skin is an entirely different organ from the skin of man." With reference to anemia, Stewart said that under compression from surface quartz applicators or other means, the depth of penetration (of ultraviolet rays) is very much greater, probably $1\frac{1}{5}$ to 1 inch (3 to 2.5 cm.) according to the completeness with which the tissue is made anemic. Bernhard is convinced of the harmful effects of the lack of light on man, as exemplified in the anemic condition of those who live on the shady side of the deep valleys of the Alps as contrasted with those who dwell where they are reached by the sun's rays.[57]

"It has been suggested that the skin lesions in pellagra indicate a light-sensitive condition in man." [15]

Voegtlin [112] referred to this possibility in the following terms:

> Raubitschek (1910) on the basis of animal experiments, advanced his very attractive photo-dynamic theory (of pellagra), which assumes that certain cereals

contain a substance which renders the skin oversensitive to sunlight. Critically viewed, none of these experiments stands the test of modern medical science.

The sites of predilection for the cutaneous lesions of pellagra are exposed surfaces. Wood [120] referred to the fact that the feet of persons who go without shoes are usually affected, and such involvement is quite common in children who go barefooted. Wood stated that he had often found lesions of the feet of women who go about the house barefooted. There would appear to be ground for the further statement that surfaces exposed during youth and the heavily pigmented genitals highly endowed for purposes of loss of heat through evaporation are not infrequent sites of pellagrous lesions, though they are not so common as habitually exposed surfaces.

In connection with an epidemic of pellagra among prisoners of war in Egypt, Enright [25] and Bigland [6] commented on the distribution of the rash in relation to exposure, but they were not in entire agreement. Enright stated:

> The rash is usually understood to be symmetrical. This symmetry, in my opinion, depended on the equal exposure of the affected areas to the sun's rays. If the exposure were greater for one limb there would be a correspondingly greater extent of the eruption on that side. I am quite satisfied that the distribution of the rash was directly proportional to the time and the extent of the exposure. For instance, in a rash on the chest—an uncommon site—the outline corresponded to the opening of the shirt. In the case of Turks, the rash on the feet was limited most accurately by the edges of the slippers worn. I have noticed that sun exposure intensified the eruption and that if the patient exposed himself too soon after the subsidence of an attack there was a great tendency to recurrence.

The Illinois Commission [46] found that sunlight played a part in producing or determining the location of lesions, as was demonstrated by having patients suspected of having pellagra wear fenestrated gloves; the eruption was largely limited to the exposed surfaces. However, many patients were seen who showed typical lesions occupying the hands and other usual areas and who "were not exposed to the direct rays of the sun at any time. Bedridden patients developed lesions in the same situations as those able to be out of doors."

Bigland's [6] observations, as well as Enright's, were made in Egypt, but at a slightly different time, and in Ottoman rather than in German prisoners, as were those cited by Enright.

Bigland stated:

> Though the sun's rays play an important part in the production of the rash, I was never able to make any skin changes appear at will, even after repeated trials with one arm bare or wearing a glove on one hand only. I cannot account for this failure.
>
> Pressure areas also show definite changes in the overlying skin, which becomes rough, thick and deeply pigmented. The commonest situations for these changes

are the external maleoli, sacrum, knees, and elbows.* Thirty-five (out of sixty-four) of the cases showed these signs, and they lasted long after other typical appearances had disappeared.

Bigland further described the skin of the patients in his cases:

> Many of the cases showed a curious fine branny desquamation over the body generally, even in the situations where a rash had not been present.
>
> One case showed a pellagrous eruption on the scrotum—interesting because this was the site where Goldberger's artificially produced pellagrins first showed the rash.

---

* Cowgill, Stucky and Rose, 1928 (reference 18), have observed the formation of ulcers on various bony prominences, particularly on the limbs, of many of their dogs subsisting on diets adequate except for vitamin B.

The remarkable symmetry in distribution of these ulcers and the fact that they were produced in animals fed on carefully controlled diets are points worthy of note. In some of their animals that were placed on the deficient diet twice, the "complete" ration being fed in the intervening period, these lesions developed twice, associated each time with the defective diet, and disappearing when vitamin B was administered. The absence of the cardinal signs of inflammation in these ulcers further indicates their malnutritional origin.

Even at the cost of digression from a subject involved, at best, the analogy presented by psoriasis in the confused etiology and others of its aspects as compared with pellagra attracts attention. Schamberg (reference 83) referred to psoriasis as an affliction which has been known since the days of the early Greeks. It appears to have certain features in common with pellagra and others of an opposite character. The similarities are more or less obvious. It appears to be opposite in age incidence, sex incidence, seasonal incidence and in the value of a diet low in protein. Hebra was in the habit of stating that patients with psoriasis are "blooming healthy individuals," and he regarded the disease as a "morbus fortium."

Outbreaks are influenced by seasonal conditions. In the climate of Philadelphia (Schamberg, reference 84), the vast majority of patients are better in summer and worse in the cold seasons. Recurrences are not uncommon with change of season in spring and fall. Psoriasis is but rarely seen in the Orient and in the tropics.

In terms of Hammett's studies, nuclear cell division is overactive, and on Hammett's principle the —SH group would be regarded as overactive. Hammett's ideas grew out of the finding that the metal lead specifically retards proliferation of the cells, and he was led to the conclusion that the metal, by precipitation, removes from activity some compound essential to the reproduction of cells. Schamberg quoted the opinion of Throne and Myers (reference 100): "Sodium thiosulphate is of no value in the treatment of patients whose blood does not show the so-called 'metallic picture'; that is, a high sugar and a low chloride content, but is of great value in those cases showing the metallic picture. In cases in which the disease process is present in large sheets or in which it is universal, they found its action helpful. Nail involvement has also responded to this line of therapy. The action of sodium thiosulphate in these cases is in removing the retained metal from regions in which it has been precipitated and in reactivating it."

Lastly, under this heading I wish to describe a condition to which only one reference could be found (Marie). In eight of the cases there was noted a peculiar seborrheic condition, chiefly around the alae nasi, sometimes scattered over the whole face. In apeparance this condition was likened to small sulphur granules raised above the surface of the skin. This was not found among non-pellagrous Turks.

In pellagra, outside of the cutaneous lesions, pigmentation has been described histologically in the medulla (Bigland,[6] p. 950, and Warnock at Abbasia), in the cortical cells of the brain, in the adventitia of the smaller vessels, in the peripheral ganglions, both spinal and sympathetic (Tuczek in 1893 [53]), and in the intestinal mucosa. Lynch (quoted by Wood [120]) described the characteristic appearance of the intestinal mucosa of the pellagrin as "the flattened, deep red or bronzed, thickened mucosa, with shallow, irregular mucosal ulcers."

THE THEORY OF A DEFICIENCY OF FOOD AS THE CAUSE OF PELLAGRA

It is not necessary to review the elaborate data on which the advocates of this theory, especially Goldberger and his associates, have based their conviction of its soundness. Though there are considerations that lead to serious question as to the sufficiency of their views, the relatively high incidence of the disease in the economically under-privileged classes,* the experimental observations, the epidemiologic studies and the measure of therapeutic success that has attended the curative and especially the preventive practice of their principles attest a genuine and fundamental influence of the factor of a deficiency of food. Goldberger and his co-workers have not attempted to state the exact nature of the deficiency, though they consider that it is probably a deficiency in amino-acids.

Wood [120] thought that it is reasonably certain that if the peasant class were provided with a generous, well balanced and varied diet, the ravages of pellagra would stop, but he regarded such a procedure as "eminently impracticable" at this time. Taylor, in his revision of Wood's article, was inclined to regard an infectious agent as also operative, but he did not question the importance of a deficiency of food.

If the essential feature of a deficiency of food is one of amino-acids, the deficiency would seem probably to be related to the recognized general limitation of the intake of protein characteristic of warm climates generally, being emphasized with the seasonally recurring

* However, the economically under-privileged classes, among the rural population at least, by reason of occupation are more definitely subject to whatever influences there may be in climatic conditions (Vance [reference 110] and many others).

temperature of summer. In this sense, the deficiency might be either in the nature of a specific lack or in the nature of a lack of stimulus to the oxidative processes of metabolism belonging to proteins generally and to certain amino-acids in special degree, which is described under the term "specific dynamic action." Such an explanation, if found to be tenable, would harmonize with the tendency so far observed in the South for the metabolic rate to decline as summer approaches, and would not be inconsistent with the view that the decline in metabolism is contributed to also by a relatively high exposure to the solar rays of summer as compared with the exposure during winter, and further would not be inconsistent with the view that any cause operating to lower the basal metabolism in this geographic area in summer favors the development of pellagra. A direct influence of solar light, without referring this influence through the intermediation of the intake of protein or the composition of food, would seem to be suggested by the rather sharp upper border of the pellagra belt and the improbability of a correspondingly sharp line of demarcation in food habits.

While the preventive and curative action of yeast as described by Goldberger may be referable to the power of yeast to increase the basal metabolism, the substitution of yeast for thyroid substance has not seemed to maintain the metabolic rate of persons with depressed metabolism in any consistent way (J. H. S.).

If the beneficial effects of the diet recommended by Goldberger are attributable to the effect on general metabolism, the claims that have been advanced for thyroid medication in the treatment for pellagra (Shelley [87] and Smith [91]) would be referable to the same mechanism.

The relative freedom of the tropics from pellagra would seem to point to the fact that neither a lowered basal metabolism nor a low intake of protein can be the essential cause of pellagra. While these conditions doubtless favor its development, more specific factors are apparently involved. It is possible that there is a combined effect of lack of a specific dynamic action of foods containing protein and the positive effect of exposure to solar rays. Even so, a deficiency in the intake of protein may be important in respect to a specific factor, such as cystine.

With reference to the various claims for an etiologic influence of alcoholism and of bacterial, parasitic and other pathologic states of the gastro-intestinal tract, if such conditions interfere with the absorption of the essential factor concerned in the deficiency of food in pellagra, these are merely modes of development of the deficiency of food, and their recognition, without assuming for them a specific toxic or infectious influence, involves no conflict with the views of those who hold to the idea of a deficiency of food as a usual and important cause of pellagra.

Similar accommodation of seemingly opposed views with reference to a deficiency of iodine in the etiology of endemic goiter has been suggested by several writers.

METABOLISM IN PELLAGRA

The chemical studies of pellagra described in the literature concern chiefly the metabolism of nitrogen, sulphur and the lipoids. The supply of sulphur, chiefly cystine, for the normal organism and its metabolic course within the organism, as far as is known, are so closely bound up with nitrogen that usually it is not possible to separate distinctly their respective rôles.*

According to Folin, the absolute quantity of creatinine eliminated in the urine of a patient on a meat-free diet is a constant quantity differing for different persons, but wholly independent of quantitative changes in the total amount of nitrogen eliminated. In pellagra, the failure of the creatinine coefficient (ratio of excretion to body weight) and of the excretion of thiocyanate (also of gastric acidity [112]) to return to normal with the return to normal of total nitrogen in the convalescent or cured pellagrin appears to indicate that restoration of a normal exogenous metabolism is not immediately, at least, accompanied by restoration of a normal endogenous metabolism.

Folin [59] found that in patients on diets relatively high in protein the normal distribution of urinary sulphur is organic, 87.8 per cent; ethereal (conjugated), 6.8 per cent, and neutral (unoxidized), 5.1 per cent. In general, the excretion of neutral sulphur is regarded as definitely characteristic of endogenous metabolism as is the excretion of creatinine. In pellagra, however, it appears that when the creatinine coefficient is low, the excretion of neutral sulphur is increased, as in poisoning caused by cyanogen.

The chief features of the metabolism of pellagra,[97] many of which are proportional to the severity of the disease, are as follows:

The general metabolism, as measured by the consumption of oxygen or the excretion of carbon dioxide, is low.

The exogenous and endogenous metabolism, as measured by the urinary excretion of nitrogenous fractions, is low.

There is an abnormal mineral metabolism, as is evidenced by a low excretion of phosphorus pentoxide.

The utilization of protein is regarded as being somewhat depressed,[97] though the observations made in Egypt did not indicate this.

---

* "We must conclude from an extensive study of the N : S ratio that this is an expression of such complex metabolic relationships as to make any idea of judging by it the nature of tissue undergoing metabolism during fasting fatuous. The most significant point, it seems, is that the relative excretion of N and S in the urine is an individual metabolic response" (Morgulis, reference 71).

There is a decrease in the thiocyanate contained in the saliva, but the normal diastatic power of the saliva is average.[94]

Gastric anacidity is common, and hypo-acidity is usual.

Intestinal putrefaction is increased (Sullivan, Stanton and Dawson [97] and Vedder [111]), but the phenols in the urine were not found to be materially altered quantitatively.[95]

The cholesterol content of the blood is increased.* [77]

The albumin-globulin ratio was reported normal in 1 case.† [82]

Hematoporphyrin is not present in the blood serum.[86]

The alkali reserve of the blood is normal.[96]

The cyanide detoxifying power remains unimpaired, provided the supply of cystine is adequate.[8]

The total amount of nitrogen in the urine is low.[97]

The ratio of urea is "low enough to suggest liver insufficiency." [97]

The uric acid content is low.

The creatinine coefficient is much below normal and remains low during convalescence. It is low in proportion to the severity of the disease as manifested clinically.[97] A report on the excretion of creatine has not been observed.

The excretion of thiocyanate is low as compared with the content of the urine at the time of the patient's discharge as being cured, but the increase during convalescence is not proportional to the increase in the total content of nitrogen.[94]

Voegtlin [112] found the amounts of ethereal sulphates, neutral sulphur, hippuric acid (Murlin, 1920) and indican increased. He regarded the purin metabolism as being normal.

Acetone and diacetic acid are not found.[9]

After a curative diet, the products of exogenous metabolism rise to approximately normal.[97]

Human milk does not show chemical changes that are considered to account for the disease in nursing infants.[112]

In 5 cases of uncomplicated pellagra, as compared with normal controls, extensive chemical analyses of the central nervous system revealed the following principal abnormalities: [52]

* "It seems not improbable that changes in the globulin-albumin ratio in plasma may have something to do with variations in sterol (cholesterol) content of plasma in disease, and even under normal physiological conditions" (Gardner and Gainsborough, reference 29).

† "Recent experiments in this laboratory show that a dilute solution of egg albumin may be changed so as to react like globulin towards ammonium sulphate after an hour's exposure, in a quartz test tube, to the light of a quartz mercury arc at a distance of 5 cm." (Clark, reference 15). However, Handovsky reported a seasonal variation in animals, with albumin relatively higher in summer and globulin in winter (Lovett, reference 65).

The water tended to increase, there was a loss of lipoids and the proteins tended to decrease slightly.

There was a decrease in the cerebrosides, phosphatides and sulphatides, which is probably due to an increased lipolytic process associated with the degeneration of the tissues.

There was a relative increase in the cholesterol content of the cerebellum and the spinal cord.

The cholesterol in the cerebrum was diminished.

The proteins seemed to be the least affected of all the constituents. They were present in normal amounts in the cerebrum and cerebellum. In the spinal cord, a decided increase was noted in the dry tissue, whereas in the fresh tissue the proteins were decreased.

There was considerable increase in extractives, which compensated for the loss of lipoids; the nitrogen-containing, noncolloidal extractives were especially responsible for the increase in extractives.

There was a loss of neutral sulphur in the cerebrum and spinal cord and an increase in this constituent in the cerebellum, "which may possibly be interpreted as a disturbance of the oxidative power of the colloidal sulphur compounds."

In a general way the spinal cord exhibits the most striking chemical changes, a fact which is in perfect agreement with histological observations (compare with Singer and Pollock, reference 90). The chemical changes in pellagra, while similar in many respects, differ from those of other diseases affecting the nervous system.

The present investigation brings out the fact that the central nervous system in pellagra is subjected to a series of considerable chemical changes involving principally certain lipoids. The study of these changes from a chemical point of view has led to a new method of characterization of this disease, which may permit to correlate them, as has been shown in the preceding investigation, with the changes experimentally produced in the nervous system of animals.

The digestive secretions [112] show some definite, although not constant, deviation from the normal. In regard to gastric secretion (Hunter, Givens and Lewis, 1916), it was found that a large number of, though not all, pellagrins suffer from anacidity and lack of pepsin. Free hydrochloric acid may be increased, normal, decreased or absent. Pepsin is absent in cases of anacidity. Children are affected in the same way as adults (Givens, 1918). There does not seem to be a relation between the severity of the disease and the degree of gastric disturbance. In some cases with anacidity and lack of pepsin, the administration of hydrochloric acid by mouth results in the secretion of pepsin.

It is interesting to call attention to several cases with anacidity which, as a result of the dietary treatment, had lost all clinical symptoms of the disease, and yet had not shown a return of the gastric secretion to normal even after several

months. This points to a more or less permanent damage to the secretory apparatus, which may possibly find its explanation in a permanent anatomical change either of the nervous innervation of the gastric glands or in the glands themselves. . . . There are certain indications that the excretion of the amino-acid nitrogen is increased in cases with gastric anacidity (Murlin, 1920), an observation which points to an imperfect cleavage of proteins in the absence of gastric digestion. The neutral sulphur fraction of the urine is also increased.

Abderhalden and Wertheimer (quoted by Lewis [59]) found that when the muscle of a frog was digested with pepsin and hydrochloric acid, the digest soon gave a strong nitroprusside reaction for mercapto groups. That the appearance of this reaction was due primarily to the activity of the pepsin was shown by comparative tests in which muscle was digested with hydrochloric acid alone. If the peptic digest was treated with alkali, the nitroprusside reaction became weak, and the addition of active trypsin did not restore the reaction to its former strength. As a result of these observations, Abderhalden suggested: "dass Pepsin und Trypsin das Eiweissmolekul an verscheidenen Stellen angreifen. Pepsin sprengt vielleicht S-S Bindungen unter Bildung der Gruppen SH, SH" (that pepsin and trypsin attack the protein molecule from different points. Perhaps pepsin decomposes S-S compounds under formation of SH, SH groups).

Lewis continued: Similar observations have been made by Harris. Egg white, which reacted negatively with nitroprusside and ammonia, gave strongly positive reactions as digestion with pepsin-hydrochloric acid proceeded. Fractionation of the digest by precipitation with ammonium sulphate showed that the proteoses, peptones and polypeptides all contained a group reactive to nitroprusside. Under anaerobic conditions, the nitroprusside reaction given by the digest persisted for several months, but in the presence of air even in an acid solution, the reactivity disappeared in a few hours, and even more rapidly in alkaline solution. During tryptic hydrolysis of egg white, the nitroprusside reaction was not observed at any stage of the hydrolysis. This might have been due to the fact that oxidation of the mercapto groups is favored by an alkaline reaction, a condition necessary for effective digestion by trypsin.

No studies of the sulphur (and cystine) content of the products formed at different stages of peptic, tryptic and ereptic digestion of sulphur-rich proteins have been made in which the newer analytical methods for proteins and amino acids have been employed. Such an investigation should throw considerable light on the problem under discussion.

A rickets-producing diet caused a definite rise in the p_H of the contents of the intestines even to alkalinity in dogs (Grayzel and

Miller), and ultraviolet irradiation (or the administration of cod liver oil) changed the reaction to the normal range, the gastric contents showing no change.[57]

GOLDBERGER AND WHEELER'S EXPERIMENTAL PELLAGRA IN WHITE MALE CONVICTS (IN MISSISSIPPI, 1920)[21]

Goldberger and Wheeler concluded that pellagra developed in at least six of their eleven volunteers as a result of the diet on which they subsisted. The relative influence of diet and solar light was apparently not taken into account in their experiment. The period during which the volunteers subsisted on the experimental diet was from April 19 to October 31, inclusive. The volunteers continued to do a share of the work on the farm, but when compared with the convicts used as controls they had shorter hours of work and regular periods of rest when in the field. They probably did not rest in the sunlight, and their exposure to light was therefore less than that of the controls and less than that of other farm laborers.

The earliest date of the beginning of a cutaneous eruption was September 12, about the end of the fifth month of the diet, or about three months after the development of certain subjective symptoms. All of the subjects lost weight, and the loss of weight was particularly marked after the development of the eruption. In the six subjects in whom the eruption developed, the initial site was the scrotum. Later, in one subject classic lesions developed on the hands and in another on the neck. In comparison with pellagra that develops spontaneously, it may be noted that: (*a*) The diet was probably a rather extreme example of the supposed pellagra-producing diet. (*b*) Though the season was favorable to maximum intensity of solar light, the exposure was somewhat less than that under normal working conditions on a farm. (*c*) Exposure during the previous winter was presumably the average of other convicts on the same farm. (*d*) All of the subjects lost weight, whereas the excellent general state of nutrition is a paradoxical feature of pellagra frequently commented on* (Goldberger and

* Generally speaking, during fasting, the basal metabolic rate is lowered along with the loss of weight, whereas in beriberi and in normal persons (Okada and his co-workers, reference 76), with vitamin B starvation and an adequate amount of carbohydrate, protein and fat, the basal metabolic rate is lowered without loss of weight and with even a gain in weight. According to these observers, the basal metabolic rate is increased by vitamin B.

In a series of limited observations, I found that the administration of yeast is followed by some increase in the basal metabolic rate; however, in a case of myxedema, which responded by elevation of the basal metabolic rate under medication with thyroid both before and after the feeding of yeast, an increase in the basal metabolic rate was not noted during the administration of yeast over a period of two weeks.

Wheeler[32]). (*e*) The lesions of the skin appeared primarily and chiefly on the genitals, which, especially in the male, is a relatively rare site.

Goldberger and Wheeler suggested that the site of at least the initial dermatitis is bound up with a specific quality of the diet. If it is assumed that in the etiology of pellagra dietary deficiency is a usual and important factor and that exposure to the solar rays of summer following relatively little exposure to these rays in winter is a usual and important factor, it would be inferred that the results obtained by Goldberger and Wheeler represented an instance of exaggerated influence of a dietary deficiency as compared with the influence of solar light, and it would be suggested as a possibility that this imbalance in causation determined the site of the major cutaneous lesions on the heavily pigmented, unexposed genitals, which are highly endowed as to function for the loss of heat through evaporation. Such an idea would receive some support from the relative frequency of genital lesions in the relatively housed female.*

EXPERIMENTAL BLACK TONGUE OF DOGS AND ITS RELATION TO PELLAGRA[32]

A synonym for black tongue is "southern canine plague." In the United States the disease is confined to the area of endemic pellagra, and Goldberger and Wheeler considered that their experimental results established "well nigh conclusively" an identity of the two conditions black tongue and pellagra. The single important difference these authors noted in the condition they succeeded in producing experimentally in dogs as compared with spontaneously arising black tongue was that, while no eruption on the external genitalia of the female dog was observed, an eruption developed on the scrotum in about 40 or 50 per cent of attacks in the male dog. Such an eruption, these authors stated, seems never to have been recorded in black tongue.

It is not possible to compare the epidemiologic features of black tongue in the male and female dog in the same way the epidemiologic features of pellagra may be compared in the different age groups of the two sexes in the human subject. However, as in the experiment on pellagra of these authors, it is to be noted that: (*a*) The diet was probably a rather extreme example of the supposed black tongue-

* Torraca, at the Mosso Institute, studied the relative effects of sunlight, shade and bandaging on the artificially inflicted wounds of guinea-pigs. The best results were obtained with the animals whose wounds were bandaged and kept in sunlight, while the wounds that were freely exposed to sunlight healed more quickly than those kept in the shade. The wounds were aseptic, so that the influence was not bactericidal (Laurens, reference 57).

producing diet. (*b*) Though the season was favorable to maximum intensity of solar light, the dogs were apparently housed in kennels inside the laboratory, which was located at the extreme upper edge of the black tongue belt (Washington). (*c*) The scrotal lesions produced in the male dog have not been recognized in the spontaneously occurring disease.

If it is assumed that in the etiology of black tongue dietary deficiency is a usual and important factor and that exposure to the solar rays of summer following relatively little exposure to these rays in winter is a usual and important factor, it would be inferred that the results obtained by Goldberger and Wheeler represent an instance of an exaggerated influence of dietary deficiency as compared with the influence of solar light, and it would be suggested as a possibility that this imbalance in causation determined the site of the lesions on the scrotum. Such an idea would receive considerable support from the failure of all observers to note scrotal lesions in the spontaneously developing disease.

Whatever may be the explanation, the predilection of the cutaneous lesions for the genitals in both experimental pellagra and experimental black tongue, in contrast to the conditions in these diseases when they arise spontaneously, is a notable feature of the reports of these investigators.

The heat regulatory function of the dog's tongue has already been referred to, and Sundstroem's observations on the function of elongation of the scrotum under experimental conditions has also been alluded to. The conspicuous lesions of experimental black tongue occurring in these organs and the conspicuous lesions of pellagra occurring in the skin and, in the experimentally produced condition, on the scrotum, the skin being the tissue chiefly concerned with the regulation of heat in the human subject, are suggestive of a metabolic disturbance common to the organs of the loss of heat in black tongue and pellagra, respectively.

An identification of black tongue with pellagra would seem to minimize to some extent the importance of economic factors in the production of the latter disease, for though the dog shares in large measure with his master, his food habits are not altogether dependent on those of his master and he enjoys a certain freedom to roam and forage according to his natural tastes and instincts.

COMPARATIVE DATA ON PELLAGRA AMONG PRISONERS OF WAR IN EGYPT

Enright,[25] in 1918, and Bigland,[6] in 1917, observed approximately the same number of pellagrins among prisoners of war at Cairo, Egypt.

the former Germans and the latter Ottomans. They came to radically different conclusions in regard to the influence of diet in the causation of the disease.* No data are available by which a comparison can be made of previous exposure to light, nor of the relative exposures about the time the disease appeared in the two groups, respectively. However, the disease developed in both groups while the prisoners were in "the Cairo district" (Cairo, Heliopolis and Maadi), and the two groups were observed at Cairo. The seasonal incidence is clearly recorded and can be compared with the pyrheliometric measurements at Cairo (Helwan)† (table 2).[50]

The pyrheliometric observations were for the period from February, 1914, to December, 1923. Thus they include the period of pellagra morbidity under discussion, but they represent average figures for the period of observation and do not cover specifically the periods of the outbreaks of pellagra. It will be noted that, with the air mass held constant, the curve of the measurements corresponds closely with

TABLE 2.—*Incidence of Pellagra Compared with Pyrheliometric Measurements*

	Nov.	Dec.	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.
Germans, 1918.....	..	..	13	11	12	14	4	2	7	..	..	..
Ottomans, 1916-1917..	1	5	23	12	10	4	Unknown	9	..	..	..	..
Pyrheliometer.....	1.23	1.27	1.31	1.28	1.22	1.16	1.13	1.12	1.13	1.15	1.17	1.19

that of the monthly incidence of pellagra, especially among the Ottomans. The observation would hardly be of significance unless supported by other data involving the same principle.‡

*Vedder (reference 111), who was invited by the Thompson-McFadden Pellagra Commission to investigate the dietary deficiency phase of pellagra in connection with the study of the commission (reference 89), found little evidence to support the theory of a deficiency of animal protein as the essential cause of pellagra. Vedder noted "that of the 82 persons in families using fresh meat daily, four, or 4.88 per cent, were pellagrins; of the 2,591 individuals in families using this food habitually, 3.74 per cent were pellagrins; and of the 263 persons never using fresh meat, only four, or 1.52 per cent, were pellagrins. Similar figures were obtained with regard to the use of eggs."

†"The pigmented appearance of the involved skin varies in different races, and in Caucasians it differs greatly in blondes and brunettes. The Egyptian shows the pigment deposit much more than the American and more than the negro, not because of a lesser degree of pigment but because of the peculiar contrast, which possibly may be due to peculiar rays of intensity in the Egyptian sunlight" (Wood, reference 120, p. 352).

‡The seasonal incidence of pellagra in the Armenian refugees at Port Said corresponded more nearly to that of the southern United States. The refugee population consisted of 4,058 men, women and children, and the customary predominance of female pellagrins (79 per cent of 653 cases) was noted. Of the 470 women and children captured with the Ottomans and brought to the neighborhood of Cairo, none contracted pellagra. Data are not available for comparing the seasonal incidence at Port Said with climatic conditions (reference 56).

The difference of opinion between Enright and Bigland in regard to the influence of diet is of interest in connection with the following comparison:

Sullivan and his co-workers [97] considered that their hospitalized patients could be divided into at least two rough classes: (1) those with marked symptoms of the skin but otherwise not much physical deterioration, a class that may be called dermal, and (2) those with moderate or slight symptoms of the skin but with general weakness, paresthesia and marked intestinal upset, a class that may be called systemic. The former showed evidences of being relatively mild. Thus a rough grouping may be made: systemic type, severe; dermal type, mild.

TABLE 3.—*Relative Influence of Dietary Deficiency and Positive Exposure to Sunlight in the Etiology of Pellagra and Black Tongue*

	Spontaneous Pellagra	Goldberger's Convicts
Dietary deficiency	±	+
Positive effect of light	±	0
Mouth and tongue	±	0
Scrotum	±	+
Mortality	Average	? if continued
	Spontaneous Black Tongue	**Goldberger's Dogs**
Dietary deficiency	±	+
Positive effect of light	±	0
Mouth and tongue	+ (name)	+
Scrotum	0	±
Mortality	Average	+ when continued
	Enright (Germans)	**Bigland (Ottomans)**
Number	65	64
Dietary deficiency	0	+
Positive effect of light *	+	0
Mouth and tongue	+ ("usually")	± (29)
Scrotum	0 (none mentioned)	+ (1)
Mortality	1.5% (65:1)	37.5% (64:24)

*Data were not available for comparison of the intensity of light in 1917 and 1918.

If the relative influence of dietary deficiency and positive exposure to sunlight in the etiology of pellagra and black tongue is allowed to remain an open question for the purpose of comparison, and if Goldberger and Wheeler's description of their experiments with convicts and dogs is taken into consideration, table 3 appears to be expressive of the relative play of the two etiologic factors and the relative results in respect to certain symptoms and mortality in the groups with spontaneous pellagra and the volunteer subjects in whom the disease was produced experimentally and in spontaneous black tongue and the dogs in which the disease was produced experimentally. In the comparison between the German and the Ottoman prisoners, the difference of opinion between Enright and Bigland has been referred to, and

there is the further interesting difference in their observations on the direct influence of exposure to light in the production of lesions on areas of the skin so exposed.

In each of the three comparisons (table 3) it would seem that when dietary deficiency is obvious and outstanding in comparison to exposure to light, the effect partakes of Sullivan's systemic type rather than his dermal type; dermal effects readily attributable to direct exposure of the affected parts to light are at a minimum; scrotal lesions are relatively high, and mortality, where it can be compared, is great.

KOCH AND VOEGTLIN'S EXPERIMENTS WITH A RESTRICTED VEGETABLE DIET IN MONKEYS

Reference has been made to the study of Koch and Voegtlin [53] of the chemical changes in the central nervous system in pellagra and

TABLE 4.—*Distribution of Sulphur, Phosphorus and Nitrogen* *

	Percentage Variation from Normal Sulphur				
	Protein	Lipoid	Neutral	Inorganic	Total
Monkey: encephalon; fresh tissue.....	— 6	—32	—40	—33	—18
Human: cerebrum; fresh tissue †.....	± 0	—31	—18	± 0	—10
Human: spinal cord; fresh tissue, mean ‡	— 5	—26	—15	—25	—16
			Extractive		
Monkey: spinal cord; fresh tissue, mean	—11	—18	— 9	....	—14

* Only the sulphur fractions are quoted here.
† Comparison of two normal cases with five cases of pellagra.
‡ Comparison of four normal cases with five cases of pellagra.

their notation of an agreement between their findings and the histologic changes observed in this condition. In connection with that study, the investigators carried out experiments on rats and monkeys, observing the chemical and histologic changes in the central nervous system as a result of the restricted vegetable diet. They noted that, in general, the changes observed corresponded somewhat closely to those observed in pellagra; in some instances, however, a considerable difference was noted. The histologic changes were similar to those found in pellagra. In their extensive investigations, the percentage of variation of sulphur from normal was studied, and the general agreement in the experimentally produced condition and in pellagra is seen in the comparison given in table 4.

The authors did not make any reference to exposure of the rats to light, nor did they ascribe any significance to the exposure of the monkeys to sunlight; nevertheless, their tables (tables 5 to 11) clearly show the extent of exposure of the monkeys.

TABLE 5.—*Monkey M I*

Diet: Corn-oil cake, 100 Gm. daily. Began feeding March 14, 1914. Body weight, 3.1 Kg.

Date	Body Weight	Comment
March 21	2.84	
27	2.66	Intense diarrhea
April 3	....	Intense diarrhea
11	2.48	Intense diarrhea
18	2.43	Looks depressed; very weak
22	....	Exposed to sunlight for 3 hours
24	....	Coughing
25	2.42	Diarrhea still persists
27	....	Exposed to sunlight for 3 hours
May 2	2.30	
6-7	....	Exposed to sunlight for 3 hours; blood vessels of ears greatly dilated
9	2.33	Diarrhea persists
11	....	Exposed to sunlight for 6 hours
12	....	Exposed to sunlight for 3 hours
15	2.28	Tongue coated; otherwise normal; exposed to sunlight for 3 hours
19	....	Exposed to sunlight for 3 hours
20	....	Diarrhea persists
20	....	Two erythematous spots in region of external canthus; nose shows erythematous spots; animal rubs nose with hands as if irritated; exposed to sunlight 1 hour; coughs
21	2.09	9 a. m., redness has much increased since yesterday; coughing; intense diarrhea; died at 1:30 p. m. while exposed to sunlight

TABLE 6.—*Monkey M II*

Diet: Corn-oil cake no. 2 (Indianapolis), 100 Gm. daily. Began feeding March 20, 1914. Body weight, 3.68 Kg.

Date	Body Weight	Comment
March 20	....	Animal has diarrhea
21	3.30	Animal has diarrhea
27	3.32	
April 2	3.12	Animal has diarrhea
3	3.07	Animal has diarrhea
18	3.00	
22	....	Exposed to sunlight for 3 hours
24	....	Diarrhea continues
25	3.05	Diarrhea continues
27	....	Exposed to sunlight for 3 hours
May 2	3.00	Diarrhea continues
7	....	Exposed to sunlight for 3 hours
9	2.92	Diarrhea continues
11	....	Exposed to sunlight for 6 hours
14	....	One hard boiled egg added to diet
15	2.89	One hard boiled egg added to diet
16	....	Diarrhea; tongue and gums normal
19-21	....	Exposed to sunlight every day, estimated 3 hours daily
23	2.66	Diarrhea continues
26	2.40	Edema of upper right eyelid
31	....	Subcutaneous hemorrhage on upper right eyelid; is very weak and looks depressed; exposed to sunlight for 30 minutes
June 4	....	Abnormal redness of gums
6	....	Animal unable to walk; intense diarrhea; died at 3 p. m.

TABLE 7.—*Monkey M III*

Diet: Equal parts of corn meal and sweet potatoes (cakes). Began feeding May 5, 1914. Body weight 2.5 Kg.

Date	Body Weight	Comment
May 9	2.32	
11	....	Exposed to sunlight for 6½ hours
12	....	Exposed to sunlight for 3 hours
15	....	Exposed to sunlight for 3 hours
16	....	Animal has diarrhea
19	....	Exposed to sunlight for 3 hours
20	....	Exposed to sunlight for 1 hour
21	....	Exposed to sunlight for 2¼ hours
22	....	Exposed to sunlight for 1½ hours
23	2.38	
29	2.42	
June 5	....	Exposed to sunlight for ½ hour
6	2.39	
13	2.39	
19	2.28	
26	1.87	Exposed to sunlight for 15 minutes
27	1.86	Had been well up to today; is sick now; cannot be roused from lying position; marked stupor; died at 9 p. m.

The data do not permit an estimation of the intensity of light to which the animals were exposed, for though the day of the year is given and the air mass is calculable, other factors, including the hour

TABLE 8.—*Monkey M IV*

Diet: Yellow corn meal (cakes). Began feeding May 5, 1914. Body weight 2.27 Kg.

Date		Body Weight	Comment
May	5	2.27	
	11	....	Exposed to sunlight 6½ hours
	12	....	Exposed to sunlight 3 hours
	15	2.18	Exposed to sunlight 3 hours
	19	....	Exposed to sunlight 3 hours
	20	....	Exposed to sunlight 1 hour
	21	....	Exposed to sunlight 2½ hours
	22	....	Exposed to sunlight 1½ hours
	23	2.12	
	29	2.07	
June	5	....	Exposed to sunlight ½ hour
	6	2.15	
	13	2.04	
	19	1.95	
	25	....	Animal has sick appearance and diarrhea
	26	1.73	Exposed to sunlight 15 minutes; lies down most of the time; looks depressed
	27	....	Cannot be aroused from stupor
	28	....	Died at 1:45 p. m.

TABLE 9.—*Monkey M V*

Diet: Yellow corn meal (cakes). Began feeding May 5, 1914. Body weight 2.8 Kg.

Date		Body Weight	Comment
May	9	2.73	
	11	....	Exposed to sunlight for 6½ hours
	12	....	Exposed to sunlight for 3½ hours
	15	2.61	Exposed to sunlight for 3 hours
	19	....	Exposed to sunlight for 3 hours
	20	....	Exposed to sunlight for 1 hour
	21	....	Exposed to sunlight for 2½ hours
	22	....	Exposed to sunlight for 1½ hours
	23	2.56	
	29	2.56	
June	5	....	Exposed to sunlight for ½ hour
	6	2.50	
	13	2.49	
	19	2.38	
	25	....	In good condition; lively
	26	2.21	Exposed to sunlight for 15 minutes
	28	....	Appears sick; lies on the floor; difficult to arouse
	29	....	Depressed; exposed to sunlight 1 hour
	30	....	8 a. m., in dying condition; 9 a. m. dead

TABLE 10.—*Monkey M VI (Control)*

Diet: Bananas, eggs, sunflower seeds, carrots, Irish potatoes and wheat bread. Body weight 2.89 Kg. Killed Sept. 16, 1914, by means of chloroform.

Necropsy

No pathologic changes noticed. Weight of fresh brain 81.59 Gm.

of the day, are lacking. If the data are redistributed so as to show the average number of hours per day of exposure and the elapsed days before the death of the monkeys, the data in table 12 are obtained.

In table 12 and chart 1 an inverse correlation is noted between the hours of exposure and the duration of life. The first animal survived

longer than the total exposure would indicate as probable. This was at a time of the year when the air filter was relatively great as compared with that when the other animals, except M II, were subjected to experimentation, but the significance of this is uncertain. Animal M VII

TABLE 11.—*Monkey M VII*

Diet: Raw carrots. Began feeding May 23, 1914. Body weight 2.5 Kg.

Date		Body Weight	Comment
May	23	2.50	
	29	2.40	
June	5	....	Exposed to sunlight ½ hour
	13	2.35	
	19	2.28	Feces soft, color of carrots
	26	2.30	Exposed to sunlight 15 minutes; skin of face shows yellowish tinge
	28	....	In good condition; lively; exposed to sunlight 1 hour
July	2	....	Diarrhea; skin shows marked yellow tinge
	3	2.21	Fed sunflower seed by mistake
	10	2.15	
	14	....	Diarrhea
	17	2.17	Diarrhea persists
	25	2.09	
Aug.	1	2.07	
	8	2.05	
	15	2.04	
	21	2.02	
	29	2.06	
Sept.	5	2.16	
	11	2.02	
	15	....	Diarrhea persists
	19	2.02	
	27	2.06	
Oct.	1	....	Fed bananas by mistake
	5	1.84	
	10	1.62	
	18	1.58	
	24	1.60	
	31	1.62	
Nov.	9	1.69	Diarrhea still persists
	12	....	Is weak
	14	1.62	Found dead at 12 M.

TABLE 12.—*Average Number of Hours per Day of Exposure and Days Elapsed Before the Death of the Monkeys*

	Diet	Season	Exposure, Total Hours	Days of Restriction	Exposure, Hours per Day
M I	Corn oil	March 21–May 21	28.00	61.0	0.46
M II	Corn oil	March 20–June 6	24.50	76.0	0.32
Average for spring				68.5	0.39
M III	Corn meal; sweet potato	May 9–June 27	21.25	49.0	0.43
M IV	Corn meal	May 5–June 28	21.25	54.0	0.39
M V	Corn meal	May 9–June 30	22.75	52.0	0.44
Average for summer				52.0	0.42
M VII	Raw carrots	May 23–Nov. 14	1.75	174.0	0.01

was fed raw carrots instead of corn oil, corn meal or corn meal and sweet potatoes, which obviously may have had an influence in the prolongation of life.

It is of further interest to note the remarks as to the appearance of the skin and mucous membranes in connection with the amount of time of exposure to sunlight (monkeys M I and M II).

Finally, the authors' note of good condition followed by prompt signs of illness after further exposure is of especial interest: M I, May 20 and 21; M III, June 26 and 27; M V, June 25, 26, 28 and 29.

These notes suggest a critical influence of the short exposures following dietary restriction and previous exposure to sunlight.* In contrast, the animal fed raw carrots and given a minimum of exposure to sunlight (M VII) does not appear to have exhibited a sudden change in condition at any time. The significance of these comparisons could be determined only by further experiment under conditions controlled as to these factors.

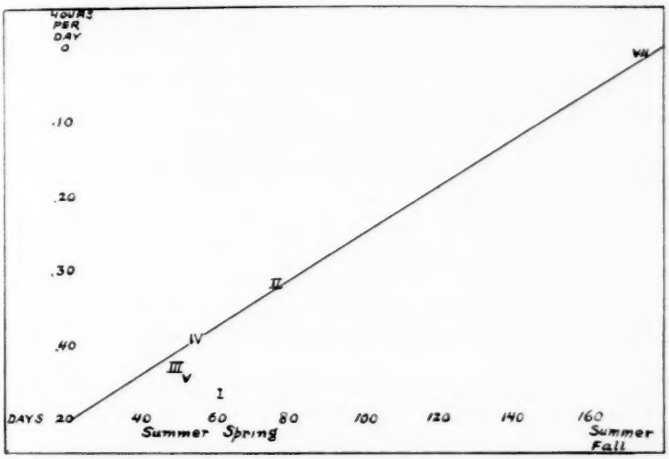


Chart 1.—The hours of exposure to sunshine per day and the duration of life in days of monkeys I, II, III, IV, V and VII in Koch and Voegtlin's experiments in the study of chemical changes in the central nervous system as a result of restricted diet of vegetables.

CREATINURIA AND THE AGE AND SEX INCIDENCE OF PELLAGRA

The relatively high incidence of pellagra in women, especially in those of the child-bearing period, suggests an examination of the metabolism of pregnancy for a possible bearing on the incidence of pellagra.

During pregnancy certain marked changes in metabolism are normally found. If the mother is given an adequate diet, gains in the amount of nitrogen are easily made in the latter half of pregnancy,[39]

* "That, indeed, exposure to intense light is capable of producing a localized hyperthermia of the central nervous organs has been borne out by the investigations of Hill and his co-workers" (Sundstroem, reference 98).

not only ample for the growth of the fetus, but resulting in a gain to the mother. This was regarded by Hoffstrom and by Wilson as a reserve store of protein to provide for the needs of lactation. Hoffstrom and also Landsberg found, as well, large positive gains in sulphur (and in phosphorus, calcium and magnesium) (Harding [39] and Macy and her associates [68]). Values for creatinine are reported by several observers to lie within normal limits. Cholesterol increases in the plasma throughout pregnancy. Ten days from delivery the changes characteristic of pregnancy have disappeared.

On the other hand, the urine is notably like that of the nonpregnant person under similar conditions, with the exception of the occurrence of creatine in the urine in the later stages of gestation [39] and for some time after. Such a finding has not been described in pellagra nor as an effect of ultraviolet radiation, and there is no evidence to relate it to the cholesterinemia characteristic of pregnancy, pellagra and ultraviolet irradiation, other than might be suggested by the fact that creatinuria and cholesteremia are characteristic of the menstrual period as well as of pregnancy.*

The origin of creatine is undetermined,[43] and therefore its appearance in the urine of women intermittently and in pregnancy is not understood. However, there are other conditions characterized by creatinuria not necessarily pathologic, which, altogether, constitute an interesting parallel between the condition and the incidence of pellagra.

Hunter [43] stated:

> While the urine of the adult male on a creatine-free diet contains no creatine, that substance is a normal and constant associate of creatinine in the urine of children of either sex up to the age of puberty.

MacLeod [67] stated:

> Creatine is present in the urine of children in considerable amount, but in that of adults only in traces. In the first years of life the creatine of boys' urine may amount to one-half the total creatine and creatinine, but it becomes gradually less and practically disappears at about seven years of age. Girls, on the other hand, continue to excrete creatine until about puberty, after which, although ordinarily absent, it reappears in the urine at each monthly sexual cycle, and is present during pregnancy and for some days after delivery. Feeding creatine to children causes it to appear in the urine, accompanied usually by a slight increase in the creatinine. The same results can be observed in women during the monthly periods, when as much as 0.1 Gm. may be present, and during pregnancy. Creatine is also present in the urine of most if not all mammalia. . . . Fasting causes the creatine and creatinine metabolism of the adult to become like that of the juvenile metabolism.

* Certain observers deny any special association of creatinuria with menstruation, though recognizing its intermittent occurrence in women (Hunter, reference 43).

Creatinuria may be induced or increased in both men and women by a great variety of experiments or pathologic conditions.[42] The most important forms of induced creatinuria are those produced by starvation, deprivation of carbohydrate (including diabetes mellitus, pancreatic diabetes and poisoning by phlorhizin, hydrazine, epinephrine or sodium selenite), wasting diseases generally, exophthalmic goiter, muscular atrophies and dystrophies and perhaps acidosis. In muscular atrophies or dystrophies, 90 per cent or more of administered creatine, even in small doses, appears unchanged in the urine (Hunter,[43] p. 603). Fontali (quoted by Hunter,[43] p. 605) found a marked creatinuria following total thyroidectomy in dogs.

Koch and Voegtlin [53] referred to another characteristic of juvenile metabolism. "During growth the relation of protein sulphur and neutral sulphur is changed to a striking degree," as is shown in table 13.

TABLE 13.—*Comparison of Neutral Sulphur with Protein Sulphur in the Brain of the Albino Rat at Different Ages*

	Protein Sulphur*	Neutral Sulphur*
1 day	30.5	48.2
10 days	44.5	45.4
20 days	56.4	28.6
40 days	63.7	18.2
120 days	61.8	18.7
210 days	63.8	14.5

* The figures represent the percentage of the total sulphur.

"During the early stages, when growth is proceeding rapidly and chemical activities may be considered to be at their height, the proportion of noncolloidal, relatively smaller, neutral sulphur molecules is at a maximum. As the tissues grow and become more highly differentiated and mature, more and more protein is laid down as structural material, and the proportion is shifted in the direction of the protein sulphur." A comparison of the cortex of man at 2 years and at maturity illustrates this point:

	Protein Sulphur	Neutral Sulphur
2 years cortex	63	22
19 years cortex	73	12

The only conclusion permitted with reference to creatinuria is that it is indicative of some departure from the relatively fixed and stable metabolism of the normal adult male. "The avidity, if it may be so expressed, of the muscle for creatine and its efficiency as a machine develop together, and as they develop, creatine disappears from the urine" (Hunter,[43] p. 611). With regard to the sexual influence, Hunter stated: "perhaps if the point were examined it would be found, as Stearns and Lewis seem to infer, that women leading a life of abundant

muscular activity exhibit no creatinuria at all" (p. 612). The athletic girl tends to minimize the apparent influence of the gonads in the metabolism of sex.

The available data appear to justify the statement that during the first years following intra-uterine life, with respect to creatinuria, the metabolism of both boys and girls resembles that of the mother. The escape of the adolescent male from this characteristic seems to be attributable to a gonadal influence, habits of exercise, food and possibly exposure to solar radiation, or to a combination of these, with or without other factors. Tonic doses of ultraviolet rays tend to establish the nitrogen equilibrium on a higher level, thus tending to "muscu-

TABLE 14.—*Race and Sex of Reported Cases*

States	Reports		White		Colored		Race and Sex Not Reported	Total Cases	Deaths	Death Rate per 100 Reported Cases
	Cards Mailed	Replies	Male	Female	Male	Female				
Virginia	2,359	823	174	302	49	103	.....	628	349	55.59
North Carolina	1,849	521	543	1,201	130	277	261	2,412	1,067	44.37
South Carolina	1,275	287	357	772	120	351	286	1,886	582	30.95
Georgia	3,022	735	985	2,142	166	575	690	4,558	1,582	34.70
Kentucky	3,601	723	159	283	15	24	32	513	220	42.88
Alabama	2,418	561	150	988	133	680	363	2,314	859	37.12
Mississippi	2,009	561	433	954	249	907	352	2,895	1,250	43.17
Louisiana	1,930	446	123	215	69	200	63	670	296	44.17
Total	18,463	4,657	2,924	6,857	931	3,117	2,041	15,870	6,205	39.1*
Colored			931	3,117						
			3,855	9,974						

	White	Colored
Male	2,924	931
Female	6,857	3,117
	9,781	4,048

* Aggregate fatality rate per hundred reported cases.

larity"; a normal diet is a necessary basis for this effect. The influence of food, work and light is almost inseparably bound up under ordinary living conditions.

It may also be noted that the tendency to creatinuria and the incidence of pellagra are inversely correlated with the functional capacity for the growth of hair as seen in beardless youth, bearded manhood and bald old age.

Possibly the tendency to creatinuria may be bound up with the fluctuations in metabolism characteristic of the menstrual cycle and pregnancy in women. The basal metabolic rate of both boys and girls is relatively high, but is subject to a sharp decline not comparable with the gradual descent of any other decade. The metabolic demands of growth are hardly constant or steady. In relation to the degree of muscularity or "active protoplasmic tissue," these fluctuations may be of significance.

The earlier data relative to race and sex incidence of pellagra in the United States are represented in table 14, from Lavinder.[58]

Bulletin 153 of the Hygienic Laboratory (table 15) gives the age and sex incidence found among the white population of the cotton-mill villages studied in 1917.

The figures of Lavinder show an incidence of pellagra in the female as compared with the male of more than 2:1, but those of the cotton-mill villages studied show that this increased incidence in the female is limited to certain age groups. In table 15 there is a notable parallel incidence of pellagra, with reference to age and sex, and the tendency to creatinuria described, which suggests that a better

TABLE 15.—*Incidence of Pellagra Among White Persons of Different Ages and Sexes in Twenty-Four South Carolina Cotton-Mill Villages During 1917 (by Age Groups Arranged to Show the Greatest Age Variations for Both Sexes)* *

Age Group	Total			Male			Female		
		Pellagrins			Pellagrins			Pellagrins	
	Total Persons†	Number	Rate per 1,000	Total Persons†	Number	Rate per 1,000	Total Persons†	Number	Rate per 1,000
All ages	22,050	1,147	52.0	10,812	483	44.7	11,238	664	59.1
Under 2 years	1,130	3	2.7	560	2	3.6	570	1	1.8
2 to 4 years	2,141	165	77.1	1,124	89	79.2	1,017	76	74.8
5 to 9 years	3,105	367	118.2	1,574	193	122.6	1,531	174	113.7
10 to 14 years	2,605	226	86.7	1,329	131	98.6	1,276	95	74.5
15 to 19 years	2,722	21	7.7	1,212	4	3.3	1,510	17	11.3
20 to 39 years	6,908	234	33.4	3,355	10	3.0	3,643	224	61.5
40 to 49 years	1,669	69	41.3	841	17	20.2	828	52	62.8
50 to 59 years	954	36	37.7	463	18	38.9	491	18	36.7
60 years and over	726	26	35.8	354	19	53.6	372	7	18.8
20 years and over	10,347	365	35.3	5,013	64	12.8	5,334	301	56.4

* From Hygienic Laboratory Bulletin, no. 103.
† As enumerated between May 1 and July 15, 1917.

understanding of creatinuria might throw further light on the etiology of pellagra. If the suggestion of Harding and Young (quoted by Hunter,[43] p. 620), that creatine is a derivative of cystine, should be confirmed, a possible influence of an error in sulphur metabolism as a factor in the etiology or course of pellagra would receive some support. In this sense it may be noted:

In the age group from 2 to 4, neither sexual characteristics nor habits of the two sexes have become sharply differentiated, and neither sex is much exposed to solar rays (male 79: female 74).

In the age group from 5 to 9, the same comparison holds approximately (122: 113).

In the age group from 10 to 14, the secondary sex characteristics are not yet fully developed, but the male is distinctly more a denizen of the open spaces (98: 74).

In the age group from 15 to 19 the menstrual function has been established in the female and apparently outbalances the influence of any climatic or other factor to which the male is exposed (3:11).

In the age group from 20 to 39, not only menstruation, but more especially pregnancy introduces profound recurring alterations in the metabolism of the female, and the incidence of pellagra assumes the ratio of 3:61. The genuineness of the influence of pregnancy seems to be borne out by a ratio in the married woman as compared to her single sister of 52:12 (Hygienic Laboratory Bulletin,[45] p. 19).

In the age group from 40 to 49, as a disturbing influence on metabolism the menopause appears to rank with menstruation and pregnancy (female 40 to 49, 62:20 to 39, 61), and "the male equivalent of the menopause," or the slowing down of the metabolic rate, is represented by an increased incidence of pellagra in this decade (male 40 to 49, 20:20 to 39, 3, resulting in a ratio between the sexes for the age period of from 40 to 49 of, male 20: female 62.

In the age group from 50 to 59, as the menstrual cycle has ceased and the child-bearing period has passed, the relatively housed existence of the female again becomes apparent in its effects, and the ratio is 38:36. After 60 years, this set of circumstances is again represented, but in sharper contrast, by a ratio of 53:18.

The foregoing paragraphs, of necessity, are presented merely as suggestive, in view of the lack of any positive knowledge as to the premises.

GEOGRAPHIC DISTRIBUTION OF PELLAGRA IN RELATION TO ISOTHERMAL LINES

It has long been observed that pellagra is a disease chiefly of north temperate latitudes. Voegtlin's map (chart 2) clearly indicates this tendency. His statement [112] of the geographic distribution is on a historical basis and is as follows: It was first discovered in northern Spain. About twenty years later, its existence was recognized in northern Italy, then in the southwestern part of France, in the Balkans, especially Roumania, and more recently in lower Egypt, Mexico, the West Indies and the United States, appearing in endemic form in all of these countries. A few sporadic cases have been reported from Great Britain, Canada, South Africa and India.

Wood's [120] statement in his article revised by Taylor describes a similar but somewhat more extended distribution:

> At the present time the countries chiefly afflicted with pellagra are Italy, Roumania, the United States, France, Spain, Egypt, Serbia, Austria. Its occurrence also in South Africa, the West Indies, Hungary, Russia, Macedonia, Bulgaria, Greece, Turkey, Algeria, Tunisia, Rhodesia, Central Africa, Asia Minor,

Persia, India, the Straits Settlements, Hawaii, Mexico, Brazil, Colombia and Argentina is noted, and in most of these countries it offers a medical problem of more than academic interest. It is said to have occurred in New Caledonia, and possibly Central America. A few cases have been noted in Korea.

Table 16 shows the approximate latitude of the countries in which pellagra is endemic and also their relation to the isothermal lines of summer and winter. These lines are also shown graphically in chart 3 for the northern and southern hemispheres, respectively. Practically all areas of endemicity lie along the isothermal line of 80 F. in summer

Chart 2.—Geographical distribution of pellagra. (After Voegtlin: U. S. Pub. Health Rep. **35**:1436 [June 18] 1920.)

(July, North; January, South), regardless of its latitudinal variations. It is also further noted that where areas of endemic pellagra occur along the line of 80 F. the isothermal belt between 40 and 50 F. winter temperature (January, North) closely approaches the curve of 80 F. for summer, and where this approximation does not occur, with minor exceptions, pellagra is not reported as endemic. The exceptions lie in the torrid zone and include southern India and the Straits Settlements in the eastern hemisphere, and Mexico, the West Indies and Hawaii in the western hemisphere.

With regard to the temperate zone, it would appear that as a result of a hot summer and a cold winter, either directly or through some influence associated with or arising out of this sequence of temperatures representing sharply contrasting seasons, pellagra tends to be endemic. With regard to the torrid zone, it is possible that the minor endemic areas of pellagra reported in this latitudinal belt are apparent rather than true exceptions to the general condition of sharply contrasting seasons. Though there is no considerable variation in the summer and winter temperatures, the land areas of southern Asia are

TABLE 16.—*Geographic Distribution of Pellagra, Showing the Approximate Latitude and the Relation to Summer and Winter Isothermal Lines*

	Approximate Latitude, Degree	Average Summer Temperature, F. (July N.) (Jan. S.)	Average Winter Temperature, F. (Jan. N.) (July S.)
Italy, northern	45 N	70-80	40
Roumania	45 N	70-80	30
United States, southern	33 N	80	40-50
France, southwestern	43 N	70-80	40-50
Spain, northern	43 N	70-80	40-50
Egypt, lower	30 N	80-90	50-60
Serbia	43 N	70-80	40
Austria, southern	47 N	70-80	30-40
South Africa	30 S	80-90	60-70
West Indies	20 N	80	70-80
Hungary	47 N	70-80	30-40
Russia, Georgia	42 N	80	40
Macedonia	40 N	80	40
Bulgaria	42 N	80	40
Greece	40 N	80	40-50
Turkey	40 N	80	50
Algeria	35 N	80-90	50-60
Tunisia	35 N	80-90	50-60
Rhodesia	20 S	80-90	70
Central Africa	10 S	80-90	80-90
Asia Minor	40 N	80	50
Persia	35 N	80-90	50-60
India, southern	10 N	80	80
Straits Settlements	0	80	80
Hawaii	20 N	70-80	70
Mexico, Yucatan	20 N	80	70
Brazil	.....	..	..
Colombia	5 N	80	70-80
Argentina	30 S	80	50-60

subject to the same seasonal reversal of currents of wind (monsoon winds) as occur in the waters of the Indian Ocean north of the equator, a southwest to northeast direction from April to October and a northeast to southwest direction from October to April. As a result, the eastern coast of southern India receives rain throughout October to April and the western coast from April to October. These conditions undoubtedly represent a seasonal variation in the amount of radiant energy received from the sun, though they are not associated with any conspicuous variation in temperature. The same considerations apply in large measure to Mexico, which, with India and the Guinea Coast of Africa, represents the areas of land surface subject to a

steady wind from one direction for six months of the year and from the opposite direction for the other six months, with the result of sharply contrasting dry and wet seasons.

The foregoing observations, though simple, present decided difficulties in interpretation. Obviously, solar rays, and probably certain features of variability in solar radiation, have an important bearing on the endemicity of pellagra. Is it a thermal influence or are the solar rays of ultraviolet wavelengths of greater significance? Whichever wavelengths are important, is their importance attributable to

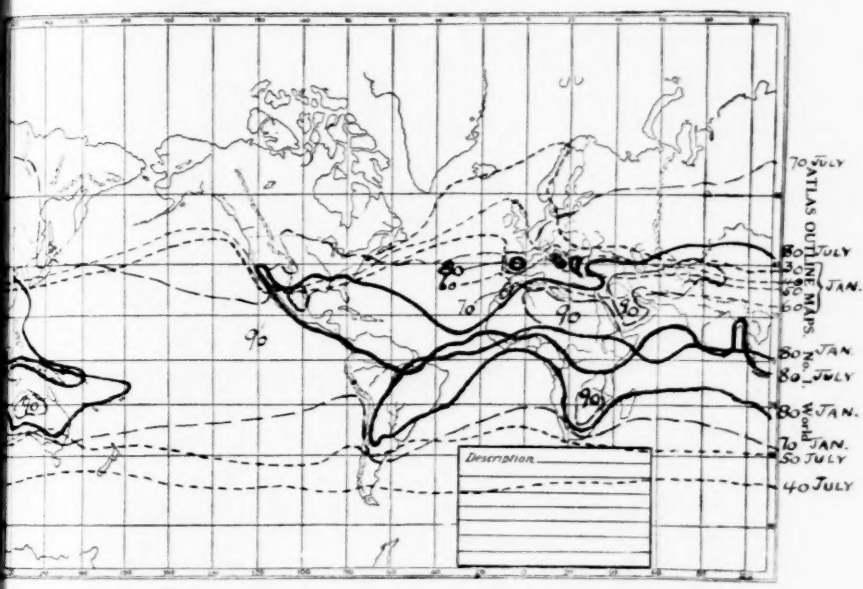


Chart 3.—Isothermal lines. The heavy, unbroken line is 80 F. summer (July, northern; January, southern), the average temperature. The long dash line is the same for 70 F. The continuous broken line enveloping numerals indicates an area of excess summer temperature, as 90. The short dash line with numerals indicates the average winter (January, northern; July, southern) temperature, as 50.

a direct effect on human metabolism or is it mediated through another influence such as plant culture? Is the climate referred to conducive to cultivation of certain crops and at the same time to the metabolic disturbances of pellagra, or does the cultivation of such crops result in exposure to solar rays of considerable intensity in summer as contrasted with low intensity in winter? Are these climatic features so

well adapted to certain crops that the population tends to pursue this particular form of agriculture to the exclusion of a more varied agriculture, resulting in a deficiency of a pellagra-preventive factor in the diet? Does the same intensive pursuit of one "money" crop (neither food for man nor feed for animals) result in an economic dependency of the population on this crop and economic depression under unfavorable market conditions? Does the consumption of one article of food as a large part of the staple diet render the population liable to a toxic or bacterial influence which the article of food may acquire under unfavorable conditions of harvesting, preparation or storage? These and doubtless other questions are involved in the observed geographic distribution of pellagra, and further data, or at least further analyses of data, are necessary for a solution of the problem. As before stated, this article attempts only to present some of the data at hand in a suggestive way.

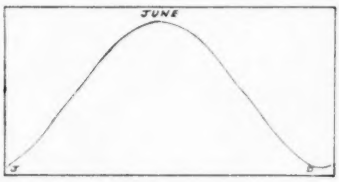


Chart 4.—Curve of the angle of the sun in the northern hemisphere.

CERTAIN FEATURES OF THE PHYSICS OF SOLAR RADIATION

The angle at which the sun's rays reach the earth is subject to diurnal and to seasonal variations. With regard to the former, suffice it to say that the maximum is at the sun's zenith, noon. The seasonal variation in the temperate zone is represented by a regular curve, with only one ascent to the maximum and one descent to the minimum during the year (chart 4). At the equator, twice a year, at the equinoxes, the sun's rays reach the earth at 90°. The minimum seasonal angle (winter solstice) for any latitude south of the arctic circle is determined by subtracting the latitude from 66° 30′. To this result the addition of 47° (the measure of the earth's surface between the tropics) gives the maximum seasonal angle of the sun for the latitude (summer solstice) (chart 5). The curve representing the sun's maximum angle throughout the year closely corresponds to the curve of mean temperature as observed in Virginia (chart 6) and also, except for the fall season, to the actual sunshine as recorded by a thermometric recorder (chart 129).

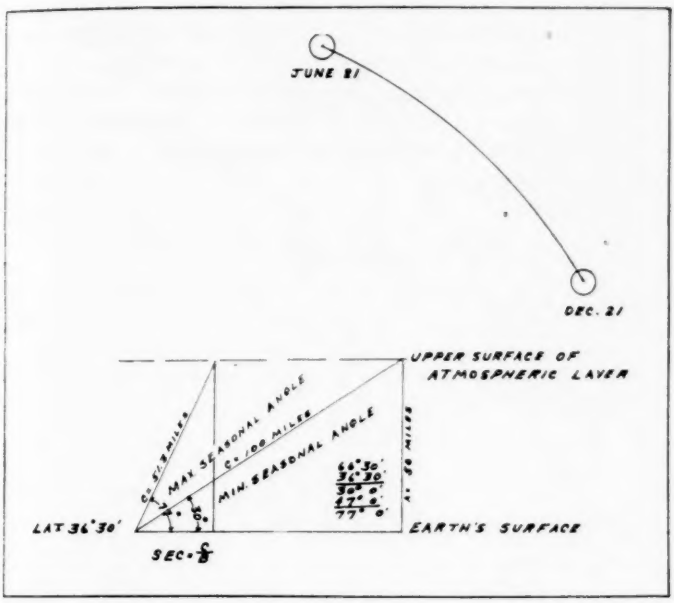


Chart 5.—Trigonometry of the air mass or length of atmospheric penetration by solar rays at latitude 36° 30′ N.

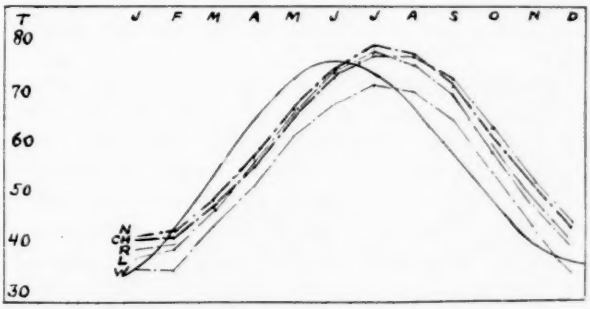


Chart 6.—Virginia. Curve of the angle of the sun. The dash dot dash line indicates the average mean temperature. The curve *CH* is for Cape Henry; *N*, Norfolk; *R*, Richmond; *L*, Lynchburg, and *W*, Wytheville.

However, in the consideration of the influence of solar rays on biologic phenomena it would seem that the atmospheric belt surrounding the earth, through which the sun's rays filter, when taken into account in connection with a varying angle of the sun, might yield values to which certain biologic phenomena would be found to correspond. If the atmospheric belt is assumed to be 50 miles in thickness, then, given the angle of the sun, the length of the hypotenuse of the triangle may be readily calculated trigonometrically by means of the sine or cosecant of the angle (charts 5 and 7). No allowance has been made for refraction of the solar rays by the earth's atmosphere or for the curvature and irregularities of the earth's surface.

If this value is plotted out for all the angles between the seasonal minimum and maximum sun's angle for latitude 33°, the curve shown

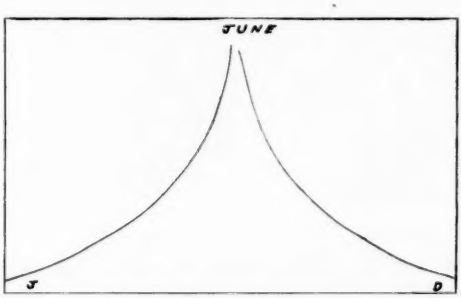


Chart 7.—Curve of the air mass or length of atmospheric penetration by solar rays at about latitude 37° N.

in chart 10 is obtained. Charts 8 to 12 show how materially the length of the solar rays' path through the earth's atmosphere is influenced by latitude.*

Considerable data have been collected on the influence of this factor of the air mass or the length of the path through the air (which hereafter will be referred to as air filter) on the intensity of solar radiation and its depletion by water vapor and by smoke and dust (Kimball [50] and Kimball [51]). The ultraviolet is most sensitive to the depleting influences of the atmospheric filter.[51] Sunlight at sea level contains from 1 to 2 per cent ultraviolet, from 43 to 53 per cent visible and from 57 to 43 per cent infra-red. Sunlight on Mount Wilson contains from 2 to 5 per cent ultraviolet, from 50 to 55 per cent visible and

* The physiologic effect of ultraviolet rays is modified by the obliquity of incidence on the surface of the body (Stewart, reference 92). The mathematical implications are the same as those applicable to the air mass penetrated by the rays.

from 48 to 40 per cent infra-red, and on Mount Whitney, from 3 to 6 per cent ultraviolet, from 54 to 55 per cent visible and from 43 to 39 per cent infra-red.

At Washington, D. C. (latitude, 38° 56′ N.; altitude, 157 meters), with average atmospheric transmissibility, but little radiation of wave-

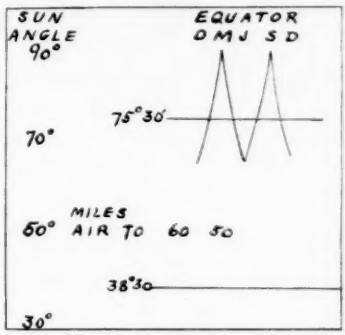


Chart 8.—Annual curve of the path of the solar rays through the earth's atmosphere at the equator. The upper curve shows the sun's angle at the summer solstice at the upper border of the pellagra belt in the United States; the lower curve, the sun's angle at the winter solstice at the lower border of the pellagra belt in the United States.

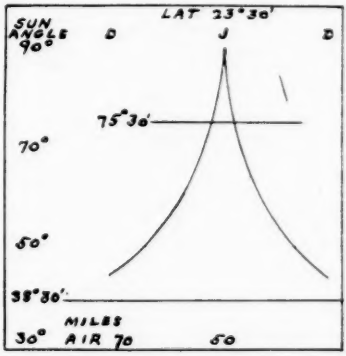


Chart 9.—Annual curve of the path of the solar rays through the earth's atmosphere at latitude 23° 30′. The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States.

lengths less than 350 mμ. penetrates to the earth's surface. On exceptionally clear days in winter, however, the receipt of this short wave radiation nearly equals that at Calama, Chile (latitude, 22° 28′ S.;

altitude, 2,250 meters), with average conditions of the sky, provided the comparison is made with the sun at equal zenith distances at the two stations.[51] It appears that the ultraviolet radiant energy in sunlight

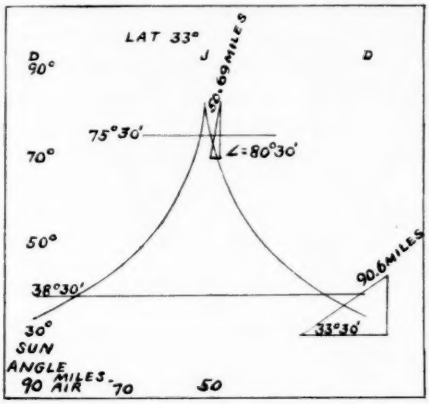


Chart 10.—Annual curve of the path of the solar rays through the earth's atmosphere at latitude 33°. The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States. The triangles show the calculation of the path at the maximum and minimum angles of the sun.

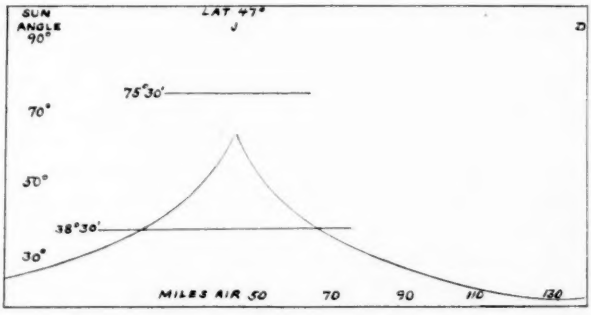


Chart 11.—Annual curve of the path of the solar rays through the earth's atmosphere at latitude 47°. The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States.

increases rapidly with an altitude above sea level and is diminished markedly by water vapor in the lower atmospheric layers. The distribution of the water vapor content of the atmosphere is such that, in general,

at sea level it tends to equalize the intensity of ultraviolet at different latitudes and at different seasons of the year.[51]

Kimball [51] gave the values shown in table 17 for wavelengths below 346 mμ., indicating the actual and relative influence of air mass and water vapor, with corrections for average dustiness.

In table 17, the numeral *1* in line *m* represents the air mass with the sun in the zenith, the numeral *2* the sun 60° distant from the zenith (angle 30°). The numerals in line *w* represent water vapor measured in terms of depth of water that would be obtained if all the water vapor in the atmosphere were precipitated. The greatly increased filtering power of smoke and dust of cities is suggested by the ratio of pyrheliometric measurements on the campus of the University of Chicago and at Madison, Wis., only 1° 18′ farther north. Taking the

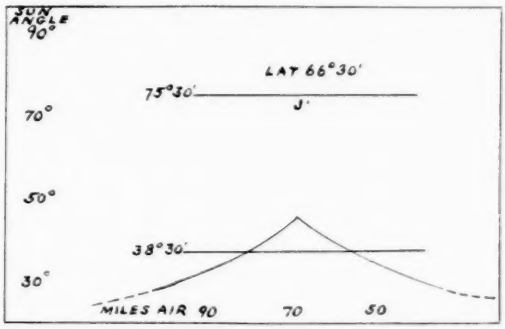


Chart 12.—Annual curve of the path of the solar rays through the earth's atmosphere at latitude 66° 30′. The upper curve indicates the sun's angle at the summer solstice and the lower curve the winter solstice at the upper and lower borders of the pellagra belt in the United States.

observations at Madison at 100, those at the University of Chicago from December to February were only 55 per cent, and in June, July and August, 84 per cent.

In many tropical towns in the British and Dutch Indies near the coast in low-lying country with high humidity and much dust, the maximum intensity (of solar radiation) is not as great as that experienced in June at midday on the coast of the North Sea.[57]

With regard to the relative influence of dry air and water vapor in depleting the ultraviolet rays of sunlight, while atmospheric pressure alters the value, with the sun in the zenith at sea level, radiant energy below wavelength 346 mμ. is only 38 per cent as intense as it was before entering the atmosphere; under the same conditions the presence

of water vapor in the amount of $w = 4$ cm. (table 17) results in a depletion to 31 per cent of the value under depletion by dry air alone.[51]

At Davos, Switzerland, Dorno observed the average midday intensity of solar heat, brightness and ultraviolet radiation by means of photo-electric cells (chart 13) (Clark,[15] p. 296). His curves not only show a midday variation for ultraviolet rays of much greater range than for heat or brightness, but that while heat and brightness * correspond to the curve of the angle of the sun (chart 4), ultraviolet intensity corresponds quite closely to the curve of the air filter (chart 7). This appears to be another demonstration of the influence of increased atmospheric mass to deplete the intensity of ultraviolet radiation and suggests that the depletion bears a direct relation to the length of the solar rays' path through the atmosphere.

TABLE 17.—*Values for Wavelengths Below 346 Mμ.*

Energy distribution in the solar spectrum; milliwatts per cm.² (dust-free air)								
m	0	0.764	0.764	0.764	1	1	1	1
w (cm.)	0	0	0.420	1.280	0	0.5	2.0	4.0
Below 346	4.2	2.3	2.1	1.6	1.6	1.4	1.0	0.5
Corrected for average dustiness								
Below 346	...	2.2	2.0	1.6	1.4	1.3	0.9	0.4
(Dust-free air)								
m	2	2	2	4	4	4		
w (cm.)	0.5	2.0	4.0	0.5	2.0	4.0		
Below 346	0.6	0.2	0.03	0.12	0.06	...		
Corrected for average dustiness								
Below 346	0.5	0.2	0.02	0.08	0.06	...		

Laurens [57] said that:

> The importance of sky radiation is very generally ignored. It is evident that the beneficial effects of sunlight are in great measure due to its luminous and infra-red portions, as Rollier, Dorno and others hold. Dorno shows that sky radiations at Davos contain, in contrast to the rest of the spectrum, from two to four times more ultraviolet shorter than 366 mμ. than does direct sunlight.
>
> Abbott also demonstrated that on Mt. Wilson skylight was several times richer in violet and ultraviolet than was direct sunlight, while Tisdall and Brown find that December skylight in Toronto has an antirachitic effect almost as marked as that obtained by exposure to the available sunlight.

While areas of approximately the same latitude are subject to approximately the same filtration of solar rays so far as this is determined by air mass, when the observations are so controlled as to hold this factor constant, it is seen that the intensity of solar radiation at normal incidence may show different seasonal trends for areas not greatly separated in latitude. Because of a possible bearing on the geographic distribution of pellagra in Italy, this seasonal variation is

* Kimball (reference 50) showed curves for total radiation that correspond more closely to the length of the path of the solar rays than to the angle of the sun.

illustrated here by the reported observations at three Italian stations. The observations are based on different air masses for the different stations, but nevertheless a constant air mass throughout the year for a given station. They are based on pyrheliometric measurements of solar intensity rather than ultraviolet radiation, but the ratio of ultraviolet to the total probably does not vary greatly at the points mentioned. The stations, their altitudes and latitudes and the periods of observation are as follows:

Naples: 149 meters, 40° 32′ N., December, 1913, to January, 1915.
Florence: 73 meters, 43° 46′ N., June, 1915, to December, 1917.
Modena: 51 meters, 44° 39′ N., March to November, 1900; July to September, 1901; January, 1902, to June, 1903.

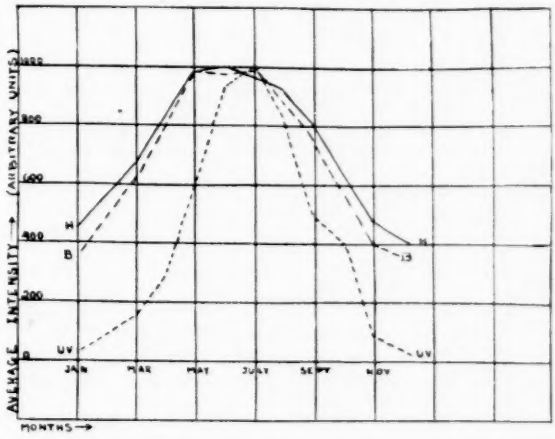


Chart 13.—Average midday intensity of solar properties. The curve *H* indicates the heat; *UV*, ultraviolet radiation; *B*, brightness, throughout the year at Davos, Switzerland. (After Dorno, quoted by Clark, J. H.: The Physiological Action of Light, Physiol. Rev. **2**:277, 1922.)

The latitudinal boundaries of Italy are approximately 47° and 37° N. A description of Christmas at Naples is suggestive of climatic conditions at the same season in Florida, 10° farther south. Reference to chart 14 reveals a maximum intensity of solar radiation in winter in Naples (for a given air mass), thus tending to offset the increasing directness of the sun's rays in summer, and a reversed condition with maximum in summer in Florence and Modena, only about 4° farther north, thus tending to accentuate the increasing directness of the sun's rays in summer. An especially sharp rise is noted in March at Florence and at Modena.

These measurements of solar intensity cannot be taken as measurements of solar light or heat received during any given period of time. Variability in the percentage of possible sunshine may occur directly with measurements of solar intensity or otherwise. This factor, in its application to the measurements at Washington, D. C., and a comparison of pyrheliometric measurements at Mount Weather, Va., and Modena, Italy, are shown in table 18 (Kimball [50]).

The average sunshine (percentage of possible) at Washington, D. C., for the twenty-seven year period of observation prior to 1920 [107] was as follows:

Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct	Nov.	Dec.	Annual
47	54	55	58	61	62	64	61	64	61	55	49	58

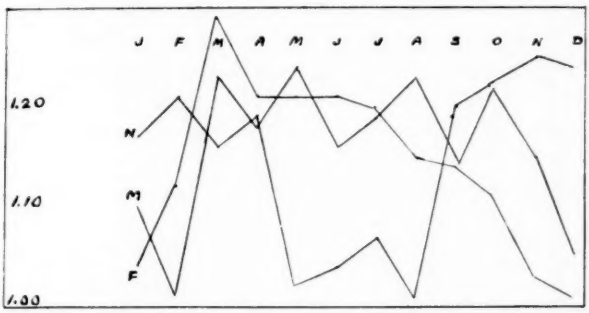


Chart 14.—Curves of the monthly means of intensity of the solar radiation at three Italian stations. The air mass was constant for each station throughout the year, but was variable in selection for different stations. The curve *N* is for Naples; *M*, Modena, and *F*, Florence. (After Kimball.)

The curves of ultraviolet radiation so far referred to deal with the physics of light as distinguished from biologic effects. There is evidence to show that the erythemal effectiveness of ultraviolet rays of different lengths varies greatly.[57] For present purposes, it is sufficient to recognize that the erythemal effectiveness of ultraviolet solar rays in general is well established. With regard to another effect of these rays, the antirachitic effect, Tisdall and Brown [101] have furnished experimental evidence of maximal diurnal and seasonal variations.

THE INFLUENCE OF SEASON AND LATITUDE ON METABOLISM

The evidence with regard to the effect of season and latitude on metabolism is conflicting and inconclusive. There are probably ample data in various laboratories to determine whether there is a seasonal

trend in the average basal metabolic rates of normal and abnormal persons in the different latitudes of the northern hemisphere.

The Far North.—While animals capable of entering on a poikilothermic state as in hibernation cannot be considered to represent conditions in the human subject, the known facts connected with the hibernation of animals suggest that in these animals the metabolism is lowest in winter. Hibernating animals sleep in the arctic night, and, save for certain nocturnal species, in general, animals sleep in the diurnal night.

During hibernation, hypoplasia of the anterior lobe of the hypophysis is found (Cushing, quoted by Wells [116]). Cannon and his associates [13] considered the sympathico-adrenal mechanism the immediate agency in the restoration of the dormant animal to activity.

TABLE 18.—*Measurements of Solar Intensity*

Washington, D. C., altitude 127 meters, latitude 38° 56′ N.												
	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
A2	1.22	1.17	1.14	1.07	0.99	0.89	0.91	0.95	1.04	1.11	1.17	1.22
Mt. Weather, Va., altitude 540 meters, latitude 39° 04′ N.												
	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
A2	1.34	1.25	1.23	1.17	0.99	1.03	0.99	1.05	1.14	1.13	1.26	1.30
Modena, Italy, altitude 51 meters, latitude 44° 39′ N.												
	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Am	1.10	1.01	1.23	1.18	1.24	1.16	1.19	1.23	1.14	1.22	1.15	1.05
A2							1.01	0.95				

Bruman [10] found a similar result after the use of atropine and considered the parasympathetic mechanism as predominantly responsible. It is possible that these observations may be consistent in view of the functional antagonism of the sympathetic and parasympathetic nervous systems and, further, that the influence of insulin and low blood sugar in bringing about an artificial state of hibernation and of injections of dextrose in terminating it [23] represents the mechanism of the sympathico-adrenal action in the natural process. Cannon and his co-workers [13] found that the conditions that increase the adrenal secretion in lower animals likewise increase metabolism in man.

The observations of Lindhard on himself, which were made while he was living in Greenland, led him to the conclusion that his metabolism, like that of the hibernating animal, was lowest in winter.* He attributed the increased metabolic activity of summer to light.

* The use of artificial radiation to offset the lack of solar radiation during the antarctic stay of the recent Byrd expedition probably precluded the collection of data relative to basal metabolism in the personnel of that expedition.

Laurens said that:

> Lindhard (Scandinavia) held that sunlight is the climatic factor which exercises the determining influence on respiration during the course of the year, the annual fluctuations in alveolar CO_2 tension being ascribed to the action of sunlight through an increase in the excitability of the center to CO_2. Sunlight was also considered the determining factor giving mountain climate its special character. . . . the consumption of oxygen and the production of carbon dioxide increased from midwinter to summer by 4 and 5.5 per cent, respectively.* The changes were similar to those observed in Greenland and on mountain tops, and to those produced by the action of C arc irradiation.

Briefly stated, the phenomena of hibernation include depression of metabolism, respiratory and pulse rates, respiratory quotient (McLeod,[97] p. 584), body temperature, blood sugar content and the function of the endocrine organs, especially the hypophysis and the adrenals. The state of hibernation does not appear to be due directly to cold. Since the time of Lavoisier (quoted by Lusk [66]), it has been recognized that cold increases the metabolism, and that in the hibernating animal a speedy transformation from the state of torpidity to one of activity occurs [22] in case the surrounding temperature falls to a low level (Britton). If the metabolism is lowest in winter in northern latitudes, it is apparently due to causes other than cold alone.†

The Tropics.—Generally speaking, the standards of normal metabolism have been derived from studies carried out in the upper levels of the north temperate zone. The reports are increasingly numerous to the effect that these standards are in excess of metabolic conditions normal to the lower levels of the north temperate zone and the zone of the tropics.[14]

With respect to temperature and sunlight, seasonal differences are least in the tropics (chart 8), and except for the possible influence of water vapor, seasonal variations in metabolism would be relatively improbable in the zone of the tropics.

Latitude of Boston and Chicago (42° N.).—Gustafson and Benedict [36] reviewed the literature relating to seasonal variations of metabolism, and in a study of eight young women in one group and five in another, at Wellesley (Massachusetts, near Boston), they obtained

---

* Lusk (reference 66), quoting Lindhard and Hasselbalch and Lindhard, stated: "The volume of respiration increases 26 per cent in summer. The intensity of the metabolic processes is not affected."

† Metabolism in the Far North may be lowest in winter without necessarily reaching its maximum in summer, the peaks possibly occurring in the fall and spring. Such an observation was recorded in one of Lindhard's subjects in 1912 (Scandinavia) (Laurens, reference 57).

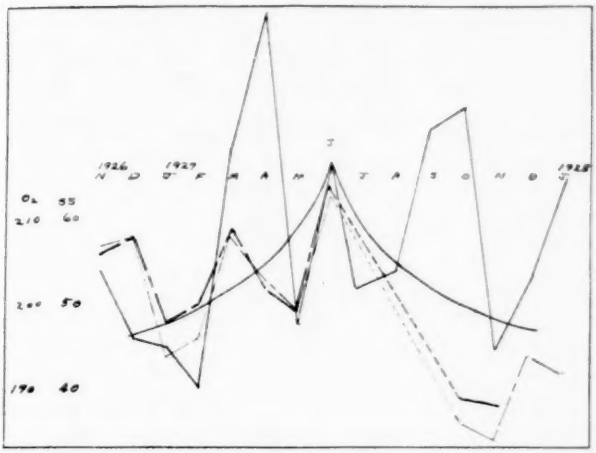


Chart 15.—The continuous line in the curve is for the sunshine at Boston, from November, 1926, to January, 1928. The heavy broken line indicates the consumption of oxygen of eight subjects at Wellesley; the light broken line, the consumption of oxygen of five subjects at Wellesley. (After Gustafson and Benedict.)

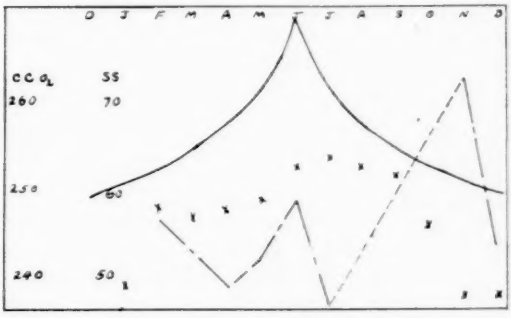


Chart 16.—*X* indicates the average sunshine at Boston. The broken line indicates the consumption of oxygen of one subject observed at Boston over six and one-fourth years. (After Benedict and Carpenter.)

similar curves for the two groups; the high peak of metabolism was found to be in June (chart 15). The variation was about 13 per cent.

The male subject observed by Benedict and Carpenter [5] over a period of six and a fourth years, at Boston, showed his highest rate in November (chart 16). The variation was about 10 per cent.

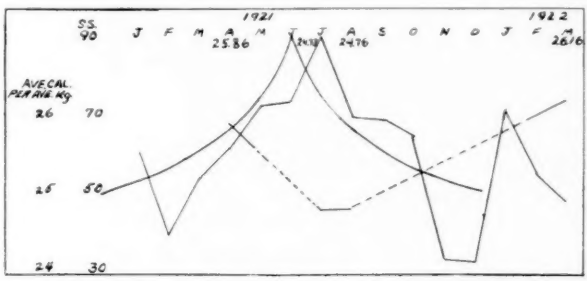


Chart 17.—The continuous line indicates the sunshine at the University of Chicago, from January, 1921, to March, 1922; the broken line, the average calories per average kilogram of one subject observed at the University of Chicago. (After Kunde.)

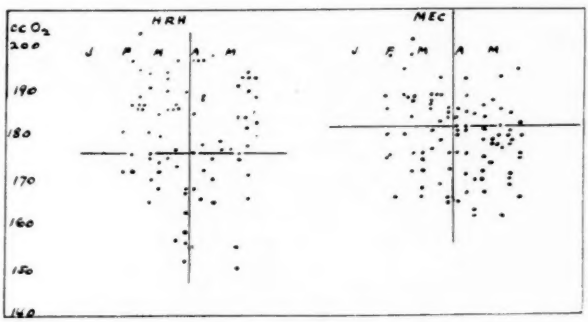


Chart 18.—The fields of dispersion and trend of daily measurements of the consumption of oxygen of two subjects at New Orleans. *HRH* indicates eighty observations, none between April 24 and May 7; *MEC*, ninety-six observations, none between February 10 and 18. (After Hafkesbring and Collett.)

The female subject observed by Kunde [55] at the University of Chicago showed her highest rate in winter (chart 17). The variation was about 5 per cent.

Thus, in this latitude, the results reported by the several observers are not consistent, but taken as a whole they might be considered consistent as a latitudinal group if further investigation should show

a reversal between the seasonal peak in latitudes farther north and farther south, respectively, as the present data seem to suggest.

Latitude of Southern United States.—At New Orleans (30° N.), Hafkesbring and Collett [37] observed a fall of about 5 per cent in the basal metabolism of two female subjects when there was a change

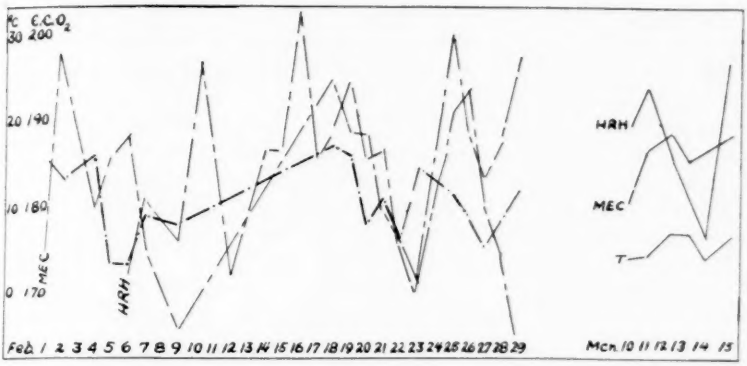


Chart 19.—The dash, dot, dash line indicates the temperature at New Orleans in 1924. The long dash, short dash line indicates the consumption of oxygen of each of two subjects at New Orleans in 1924 (February). Curve *T* indicates the temperature; *HRH* and *MEC*, the consumption of oxygen in March, 1924. (After Hafkesbring and Collett.)

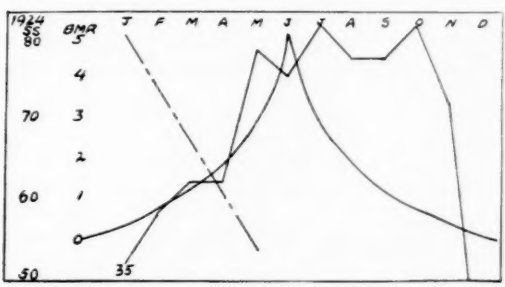


Chart 20.—The continuous line indicates the cloud at New Orleans in 1924; the long dash, short dash line, the metabolic rate (decline) from "cold" weather to "hot" weather at New Orleans. (After Hafkesbring and Collett.)

from cold weather to hot weather. Chart 18 shows the trend and the fields of dispersion. Whether or not the observed fall from February to May was actually due to the increasing temperature of the air is open to question. Day by day in February the conspicuous tendency in both subjects was for the metabolism to rise and fall with a rise

and fall of the temperature of the air (chart 19). Somewhat the same diurnal trend is shown in March. While a comparison by months shows a fall of metabolism with a rise of temperature (charts 18, 19 and 20), there are other climatic factors, including an increased percentage of sunshine and an increased angle of incidence of the sun's rays (a decreased air filter), that possibly should be considered as bearing on the fall in metabolism from February to May.*

A lowered intake of protein with an increasing temperature would appear to be a probable factor in the seasonal decline and in the generally lower rates found in warm climates. In certain sections of the population, this factor may be exaggerated by economic conditions, as described by Goldberger and his associates. On the other hand, given even a moderate intake of protein, its specific dynamic action is definitely enhanced at temperatures prevailing during the summer in the south (Lusk,[66] p. 234).

Rubner said that:

> One hundred grams of meat did not change the metabolism at 20°, 25° or 30°; 200 grams of meat had no effect at 20° or at 7°, but at 25° and 30° there was an increase, although the food contained fewer calories than the requirement. With 320 grams of meat there was a great increase above the starvation requirement, except at 7°, where it is a maintenance diet and the metabolism remains unchanged. In other words, at a temperature of 30° the specific dynamic action of this amount of protein is capable of increasing the heat production above that of starvation by about 53 per cent, while at 7° there is no change whatever. It is also evident that at a high temperature even a small amount of protein, such as 200 grams of meat, causes a considerable rise of metabolism.

The suggestion that basal metabolism may be influenced by the solar rays appears to receive some support from the observations in

---

* Comparisons of this kind cannot be made without a consideration of the extent of exposure of the subjects to the prevailing external atmospheric conditions, and the relative influence of these external conditions as compared with the influence of the indoor conditions at the time of the observation.

The metabolism determined inside the house and that determined in the open, lying naked on the sand, usually show an increase for the latter, depending, it seems, on chemical regulation of the loss of the heat. The increase is observed when the sun is not shining, as well as when it is, but always occurs when there is a wind, so that it is most probably due to stimulation of the skin (Laurens, reference 57).

Kestner and his co-workers found that the sun at the seashore (and quartz mercury and carbon arc lamp radiation) strongly and immediately increases gaseous metabolism by its action on the skin, though the increase is diminished if there is a simultaneous heating effect, which brings the chemical heat-regulating mechanism into action. The effect is specific, being called forth by a stimulus to the skin. These observers reported that the basal metabolism was increased at high altitude in winter, but not in summer, and although it also occurred in the absence of sunlight it was much greater when the hands and face were exposed to the sun.

Virginia. They are limited and are open to the criticism that the determinations of metabolism were not made on subjects selected as normal. The latter criticism is less valid as against the ultimate purpose in view, the demonstration of a reversed correlation between the average basal metabolism of subnormal persons on the one hand and the intensity of solar rays on the other hand, with special reference to the etiology of pellagra.

It has been brought out that the filtering of ultraviolet rays varies with the curve of the air mass and with the amount of water vapor in the atmosphere. It follows that these rays are of greater intensity at the summer solstice, with a minimum of water vapor. With reference to the air mass filter, Dr. P. S. Smith, in a personal communication, reported that for 1928 the average basal metabolic rates * (272) taken in the clinic at Abingdon, Va. (latitude, 37° N.), reached a low level in June. Examination of his curve (chart 21) shows that the general trend is directly with the seasonal decreasing and increasing air filter. Further, as to water vapor,† it is seen that after the summer solstice the curve of the average metabolic rate tends to be deflected upward and downward away from the curve of the air filter to correspond with a rise or fall in cloudiness. In other words, the curve of metabolism varies inversely with the intensity of solar radiation.

At Richmond, Va. (latitude, 37° 32′), the same trends are noted. The combined determinations of metabolic rate (1,976) for the years 1926, 1927 and 1928 are shown in chart 22. The rise in August to correspond with the rise in cloudiness is noticeable. Since August is quite consistently a cloudy month in this geographic area, it is interesting to note a consistent rise in the metabolic rate, which was higher than in either July or September, in each year of the three years. Reference to the relative low level of the average metabolism reached in the several years will be deferred until reference is made to the influence of a relatively cloudy winter season.

From studies made on white men, chiefly physicians, and on Negro laborers in Brazil (Rio de Janeiro, latitude, 22° 54′ S.), Almeida (quoted by Dubois [22]) suggested that in sufficient time all of the factors that modify the total metabolism will finally alter the value of the basal metabolism. According to Almeida, the basal metabolism depends on all the factors which in passing have modified the intensity of the habitual metabolism. Among these are muscular work, the level of the

* All rates above plus 20 being omitted so as to exclude definite hyperthyroidism.

† For the present, reference to relative humidity was omitted, and only cloudiness was considered as it was observed at the nearest United States Weather Bureau station, Wytheville, Va., sixty miles distant.

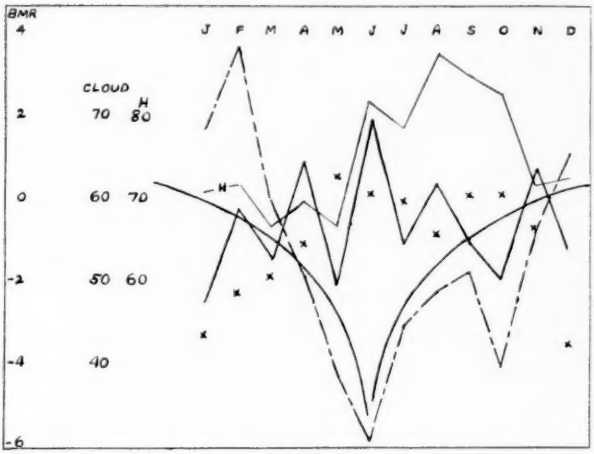


Chart 21.—Southwest Virginia. *X* indicates the average sunshine at Wytheville; the two continuous curve lines, the curve of atmospheric filter, reversed; curve *H*, the humidity at Wytheville in 1928; the continuous lines, cloudiness at Wytheville in 1928, and the broken line, the average basal metabolic rates at Abingdon, monthly, in 1928 (total determinations, 272).

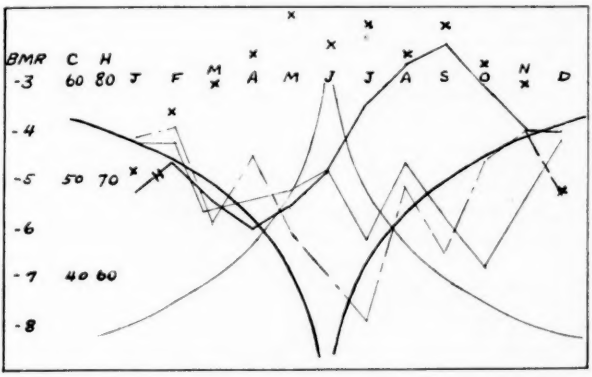


Chart 22.—*X* indicates the average sunshine at Richmond; the continuous curves, the curve of atmospheric filter; curve *H*, the average humidity at Richmond in 1926, 1927 and 1928; the continuous line, the average cloudiness at Richmond in 1926, 1927 and 1928, and the broken line, the average basal metabolic rates at Richmond, monthly, in 1926, 1927 and 1928 (total determinations, 1,976).

intake of food and the difference between the temperature of the body and the temperature of the air multiplied by the surface area. In the tropics, all of these levels are lower than those in the temperate zone. These ideas lead readily to the consideration of a hereditary level of metabolism or a genetic factor affecting the habitual rate.

The cotton-mill worker is the lineal descendant, and often merely the transplanted self, of the rural laborer of the southern part of the United States.

There has been recent experimental evidence to show that under certain circumstances rats may acquire and transmit to their progeny a capacity for growth and maintenance of nutrition devoid of vitamin B.[54] In contrast to this adaptation, it would not seem contrary to biologic phenomena generally if a nutritive lack and a resulting metabolic depression were handed down from one generation to another. Such a feature seems to be exemplified in the epidemiology of endemic goiter.

If, as Almeida supposes, in sufficient time all of the factors that modify the total metabolism and in passing have modified the habitual metabolism will finally alter the value of the basal metabolism, it would appear that a perpetuation of factors tending to lower habitual and basal metabolism in the individuals of several generations would, in sufficient time, result in a level of metabolism which would constitute a characteristic that would tend to be passed on from one generation to another. Such a conception could well include a specific nutritive lack as tending to the development of pellagra. The characteristic in successive generations would not constitute an acquired character in the strict sense of persistence after the determining influences had ceased to operate, as the absence of the pellagra-preventive factor supposedly persists in the succeeding generations.

On this basis, possibly an explanation may be reached of the more recent observations that, contrary to earlier opinion, pellagra is not rare in children in the United States (Hygienic Laboratory Bulletin 153, p. 15). The children born of the first generation of pellagrous parents may well show an incidence of the disease differing from its incidence in children of countries such as Italy, where pellagra has been endemic for many generations and where the disease is considered to be rare in children under 15 years of age.

In view of the historic prevalence of pellagra in certain Mediterranean countries, including Italy, and the comparatively recent development of the disease in endemic form in the United States, it would be of interest to note whether immigrants coming directly from areas where the disease is endemic, for example, in northern Italy, to

the southern part of the United States exhibit a tendency to the development of pellagra more promptly than was shown by the peoples from northern Europe and equatorial Africa, by whom the southern states were settled and among whom pellagra did not appear in endemic form for several generations.

Whether or not a different source of immigration might have resulted in an earlier appearance of pellagra in endemic form in the southern part of the United States, it hardly seems to conform to the data of the social and economic history of the South to suppose that food habits or food supplies in this area changed radically in the forty years elapsing from the time of the war between the states until 1907.[8] On the other hand, the time estimated by Goldberger and his associates for the influence of a deficiency of food to become operative in the production of pellagra is in terms of weeks or months only. Food, occupation and climatic factors do not appear to have undergone a sudden radical and pellagra-producing change.

Under these circumstances it would seem necessary to assume the invasion of some infectious agent or the influence of some factor operating over a period of several generations with increasing intensity so as to result in the appearance of an endemic disease in 1907, which was hitherto unknown in this area except in sporadic form. In view of the failure of well directed efforts to establish an infectious etiology, no other assumption seems to fulfil the conditions so well as the postulation of a genetic factor.

Definition of Cloudiness.—Though cloudiness and sunshine are in a real sense opposite values, according to the standards of the United States Weather Bureau, they are not exactly so. Theoretically, 30 per cent of sunshine would be the equivalent of 70 per cent of cloudiness. Actually, by the methods of the Bureau,* they may be equivalent

* The Bureau describes its methods of observation as follows: "The following tables give sunshine for 148 stations (1914), the monthly amounts of sunshine and percentage of the possible as derived from the automatic records made by an instrument designated the 'thermometric recorder' illustrated in the preceding volumes of this series. This instrument does not record satisfactorily the duration of sunshine for about one hour after sunrise and for about one hour before sunset, and on this account it has been considered necessary to apply to the record for these hours what has been designated a 'twilight correction.' The amount of this correction is found by noting the comparative cloudiness of the sky during the time that elapses between the hour of sunrise and the moment the instrument begins to record and between the time the instrument ceases to act and the hour of sunset. The average cloudiness of the whole sky is determined by numerous personal observations at all stations during the day time, and is given in the column 'Daylight' under cloudiness in the tables of Part III" (United States Weather Bureau Annual Report).

or they may vary as much as 15 per cent, as is illustrated by the month of December, 1921:

	Sunshine	Theoretical Cloudiness	Actual Cloudiness	Variation
Wytheville, Va.	34%	66%	66%	0
Charleston, S. C.....	74%	26%	41%	15%

Therefore, while it is legitimate to reverse a vertical scale for cloudiness and present the largest figures at the bottom so that a rise in curves represents a relative increase in sunshine, the reversed scale for cloudiness cannot be used for an exact representation of sunshine.

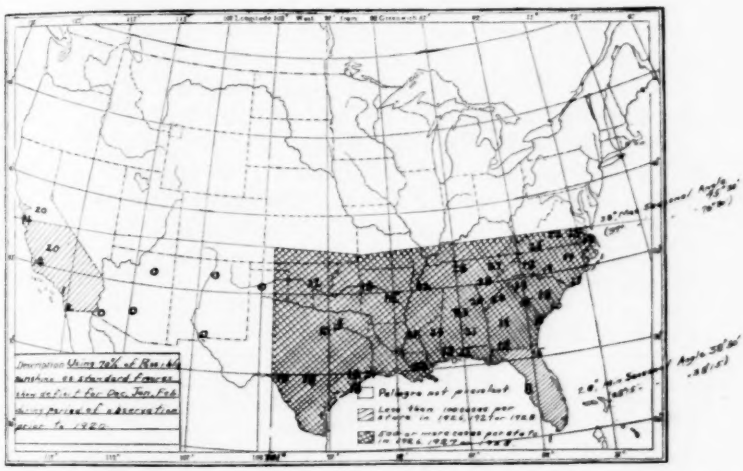


Chart 23.—The shading represents the prevalence and distribution of pellagra in the southern United States in 1926, 1927 and 1928. The numerals indicate the deficit of sunshine for December, January and February, during the period of observation prior to 1920, 70 per cent of possible sunshine being used as a standard. (From Bull. W. U. S. Weather Bureau.)

ACCUSTOMED RADIANT ENERGY AND DEVIATION THEREFROM

The stationary population of any given area of the earth's surface is subject to deviation in at least three ways in the amount of radiation received from the sun: (1) variation in the altitude of the sun and the thickness of the air filter (annual regularity and seasonal variation); (2) variation in cloudiness (annual irregularity and seasonal irregularity) and (3) variation in exposure to the available sun in winter and to the inevitable sun in summer (annual irregularity and seasonal irregularity).

Laurens [57] found the metabolic effects of ultraviolet irradiation to be of greatest significance when taken into account with the accustomed exposure to these rays, and he concluded that probably any deviation from the usual, so far as radiant energy is concerned, acts as a stimulus that disturbs the metabolism of nitrogen, calcium and phosphorus.

It is now proposed to examine certain features of pellagra as it occurs in the southern part of the United States with reference to the idea that, so far as radiant energy is concerned, there may be a critical maximum of exposure to solar rays beyond which a disturbance of metabolism conducive to pellagra results if the recent previous exposure has fallen below a critical minimum of safety (under certain abnormal conditions of nutrition); as a corollary, the least minus deviation of exposure to the available solar rays in winter and the least plus deviation of exposure to the inevitable solar rays in spring, summer and fall (within the parallels of latitude rendered critical by the earth's seasonal position in relation to the sun) probably tend to avoid such disturbances of metabolism as are conducive to pellagra.* Any difficulty arising from the involved construction of this paragraph may be somewhat relieved by recalling the principles underlying sunburn.

The upper limit of the pellagra belt in the United States is defined approximately by latitude 38° N., at which the maximal seasonal angle of the sun is 75° 30′.

---

* For any given latitude the number of days the sun's angle is above or below a given degree at a given hour may be calculated, and the number of hours at which the angle is above or below a given degree may be calculated for any latitude at any season. Since the physiologic effect of irradiation is one of intensity multiplied by time (Warren, reference 115), both are to be taken into account. The element of time is involved in the amount of exposure as determined by occupation or other factors, as, for example, in the planting of cotton, and the element of intensity is involved in the fact that this crop is planted at or near the summer solstice. The tentative assumption is:

Duration of elapsed time above a critical minimal angle is protective; duration of elapsed time below a certain minimal angle is sensitizing. Work in cotton-mills involves the principle of duration of time below the critical minimum.

If the zone of pellagra in the northern hemisphere is between latitude 38° and 30°, with a minimum seasonal angle of the sun of 28° 30′ to 36° 30′, and a maximum of 75° 30′ to 83° 30′, and if 34° is taken as the focal latitude and 36° 30′ as the protective minimum, the minimum for 34° is 32° 30′, 4° below the protective minimum, and since the sun travels 47° in 182.5 days, it is (at 34° latitude, with a minimum altitude of 32° 30′) below the protective minimum of 36° 30′ thirty-one days ($2 \times 4 = 8$ degrees) ($8 : 47 :: \times : 182.5$) in the year. At the upper latitude of 38°, a longer period elapses below the protective minimum, but the period above the critical maximum is not so great. If 50 miles is assumed to be the depth of the atmosphere, the difference in the atmospheric belt traveled by the sun's rays at an angle of 32° 30′ (latitude 34°) and 26° 30′ (latitude 40°), respectively, is 18.85 miles longer filter at latitude 40° (112.05 miles minus 93.2 miles), and the difference at 32° 30′ and 26° 30′ is 1.3 miles (52.1 minus 50.8).

The lower limit of the belt is defined approximately by latitude 28° N., at which the minimal seasonal angle of the sun is 38° 30′ (chart 23).

So far as the sun's angle is concerned, it would be inferred that solar rays have a pellagra-producing effect in areas receiving them at an angle of 75° 30′ or above, but in view of the relatively low prevalence of the disease in the tropics, a more efficient pellagra-preventive effect would be attributed to solar rays reaching the earth's surface at no time of the year below an angle of 38° 30′* (Voegtlin's map, chart 2).

A pellagra-preventive influence ascribed to a minimal seasonal angle not falling below a critical point tends to be supported by the fact that, within the pellagra belt, if the sunshine of a given area is maintained at or above 70 per cent of the possible sunshine for the time of and following the winter solstice, December, January and February,† pellagra is not prevalent. By virtue of the absence of cloudiness, the solar rays received during the winter appear to have a protective influence of the same order as a minimal angle above the critical point, though this apparent protective influence of winter sunshine cannot be appraised without further consideration of relative densities of population (relatively sparse between longitudes 101° and 105° W.) and the economic pursuits of the people. On the other hand, since in the United States the area apparently protected by a relatively high minimal angle of the sun in winter (Florida) is also relatively high in winter sunshine, confirmation of a supposed protection from a high minimal angle would have to be sought in areas farther south with a deficit of winter sunshine. However, the principle of protection by exposure to a total of solar rays not falling below a minimum does not seem to be involved in these distinctions.

---

*The idea may be somewhat clearer if stated in terms of the adjacent side of the triangle rather than the angle itself or the hypotenuse. To those familiar with the folklore of the southern United States, the statement will be reminiscent of the rule concerning the ground-hog often quoted in connection with the second day of February.

If one is accustomed not to cast a shadow of less than two and one-half times one's stride at noon during most of the winter and is rather accustomed (actually) to cast a shadow of one-half one's stride or less at noon during the summer (5 : 1, or for a man 6 feet tall, 90 inches : 18 inches), one may not with impunity incur the deficiency of diet described by Goldberger.

†Possibly a shift of attention from the cloud of the three months December, January and February would reveal a sharper index than these three months. For example, the unusual cloudiness of February, 1927, throughout nearly the whole South appears to correlate better with the incidence of pellagra during that year as compared with the cloudiness of February, 1926, and the incidence of pellagra in that year (chart 24).

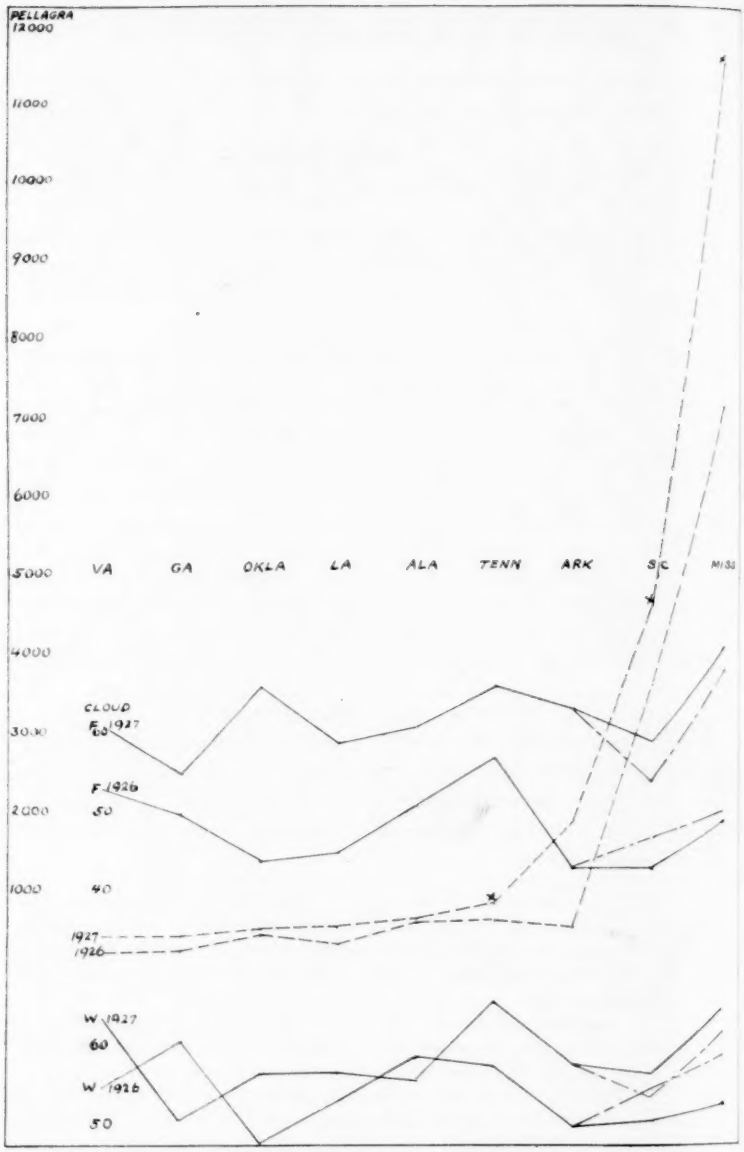


Chart 24.—Nine states. Curve *W* indicates the winter cloudiness for 1926 and 1927, using observations at all stations except for South Carolina, Greenville only, and for Mississippi, Memphis only; the continuous and broken curves *W*, same, using observations at all stations in each state. The continuous broken line indicates the incidence of pellagra in 1926 and 1927. *F* indicates the February cloudiness for 1926 and 1927, using observations at all stations except for South Carolina and Mississippi, Greenville and Memphis only; the continuous and broken curves *F*, the same, using observations at all stations in each state.

A sharp definition of the upper border of the pellagra belt in the United States seems to be supported by its distribution in the state of Virginia (chart 25) and Kentucky (chart 26) and a comparison of Arkansas and Oklahoma with Missouri and Kansas.*

The sharp break in the pellagra belt shown at longitude 101° W. is based on the reports of the distribution and prevalence of pellagra in Texas for the period from 1907 to 1911-28 (chart 27).

Examination of chart 23 shows that within the pellagra belt in the United States, in areas where there was no deficit of winter sunshine below 70 per cent of the possible sunshine (longitudes from 101° to 105° W.), pellagra is not prevalent, that where there is a slight

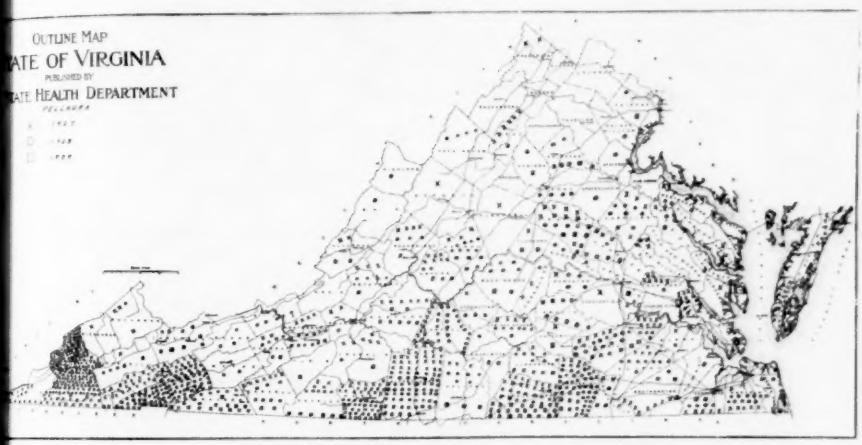


Chart 25.—Incidence and distribution of pellagra in Virginia in 1927, 1928 and 1929. (From the Virginia State Board of Health.)

deficit below 70 per cent but not as much as 10 per cent (Florida and California), there were less than 100 cases of pellagra per state reported

* All data relative to the incidence, distribution and prevalence of pellagra in the United States are derived from the United States Public Health Reports and reports of the State Boards of Health. While the data are based chiefly on returns from practicing physicians and are generally conceded to be incomplete, there appears to be a probability of average error which would equalize the application of the figures. In instances in which careful enumeration has been made by official agencies (Hygienic Laboratory Bulletin, reference 45), the data are in general agreement with those from the sources generally used herein. Statistics gathered by direct observation, as those of the Hygienic Laboratory, would be expected to represent more accurately the actual development of the disease than reports compiled from the data furnished by practicing physicians; however, there is but little noticeable variation between the seasonal incidence as represented by the two classes of statistics.

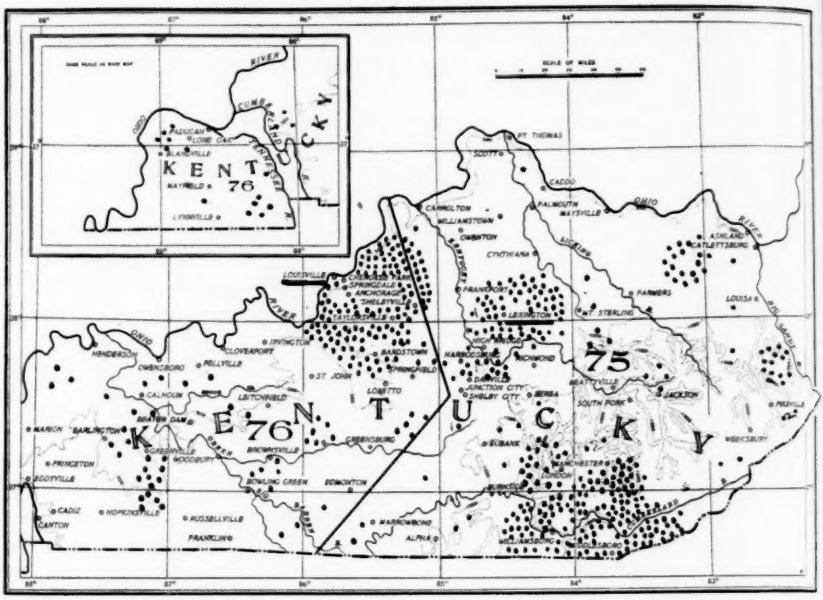


Chart 26.—Incidence and distribution of pellagra in Kentucky from 1907 to 1911, inclusive. (After Lavinder.)

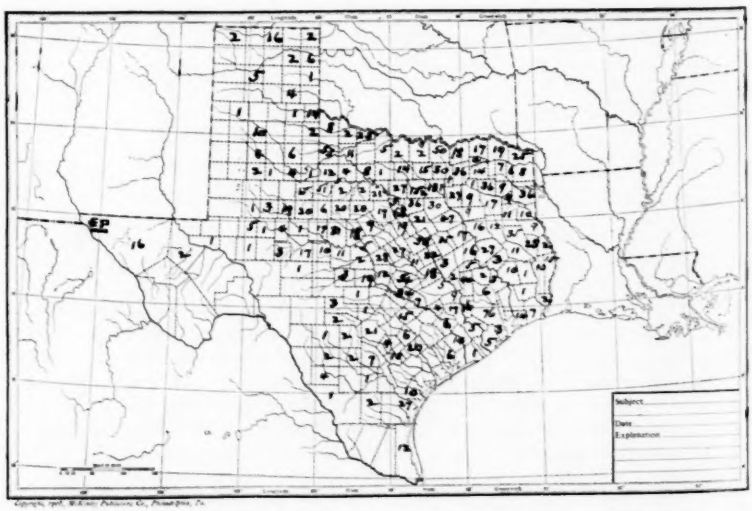


Chart 27.—Incidence and distribution of pellagra in Texas, from 1907 to 1911, inclusive. (After Lavinder.)

in any year from 1926 to 1928, inclusive, and that in areas where there was a deficit of winter sunshine of from 10 to 27 per cent below the standard of 70 per cent (from the Atlantic coast to longitude 101° W.), there were 500 or more cases of pellagra per state for each of the years 1926, 1927 and 1928.

THE SEASONAL INCIDENCE OF PELLAGRA IN NINE SOUTHERN STATES, FROM 1925 TO 1929, INCLUSIVE, IN RELATION TO SOLAR RADIATION

The data on the seasonal incidence of pellagra in nine southern states are plotted in charts 28 to 69.* The relatively low incidence of pellagra in Florida and California (less than 100 cases a year reported) renders

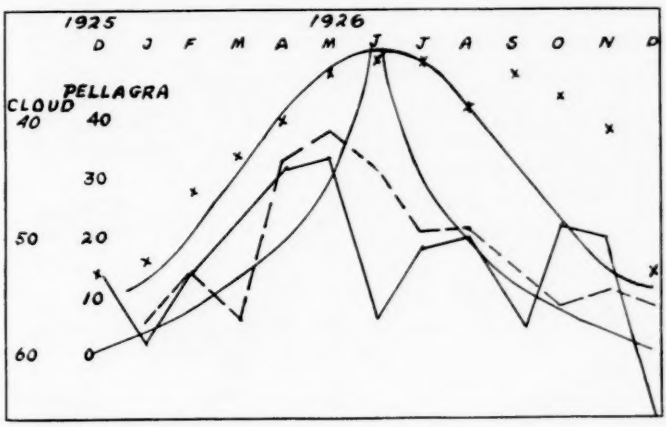


Chart 28.—Virginia, 1926. In this chart and charts 29 to 60, *x* indicates the average sunshine at all stations for the period of observation. The continuous curves indicates the curve of the angle of the sun. The two continuous curves indicate the curve of the air mass or air filter. The continuous line indicates the average of cloudiness at all stations; the broken line, the monthly incidence of pellagra.

them unsuitable for purposes of statistical study, and they are excluded from general statements.

The striking feature of the charts is the tendency for the seasonal incidence of pellagra to rise and fall with the decreasing and increasing air filter; if the curve of ultraviolet intensity at Davos is considered as applicable to these states, the tendency is for the seasonal incidence of pellagra to rise and fall with increasing and decreasing intensity of

* The curve of the percentage of cloudiness for each state was obtained as a result of the average of all stations reporting from the state.

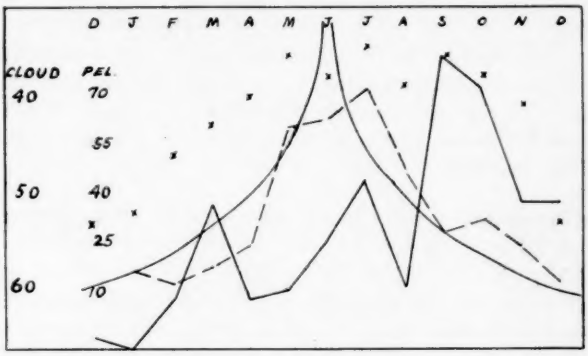


Chart 29.—Virginia, 1927.

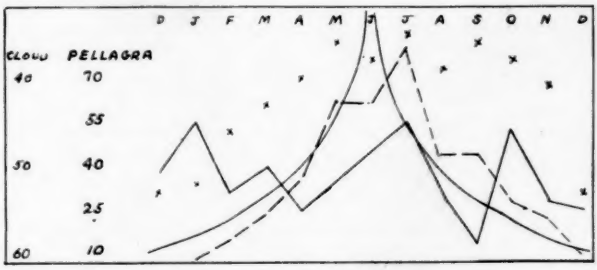


Chart 30.—Virginia, 1928.

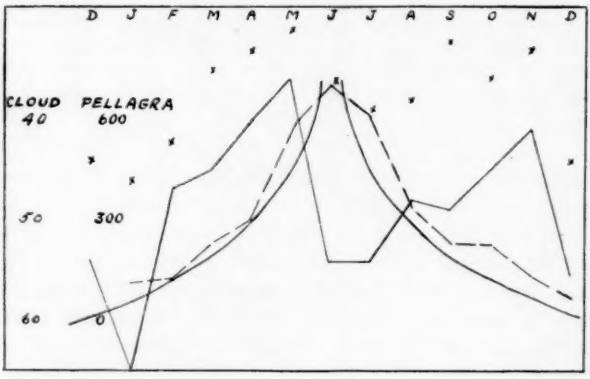


Chart 31.—South Carolina, 1926.

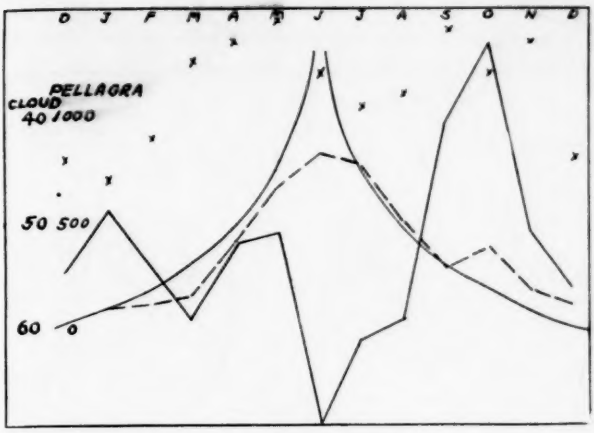


Chart 32.—South Carolina, 1927.

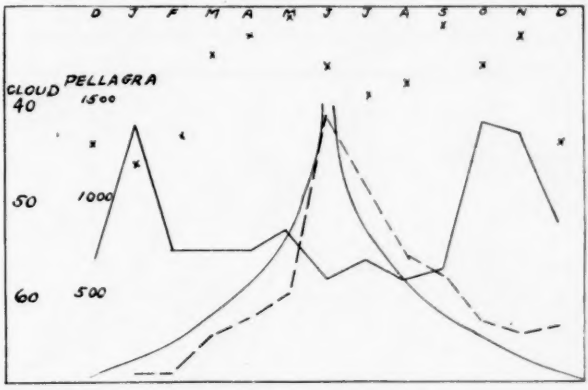


Chart 33.—South Carolina, 1928.

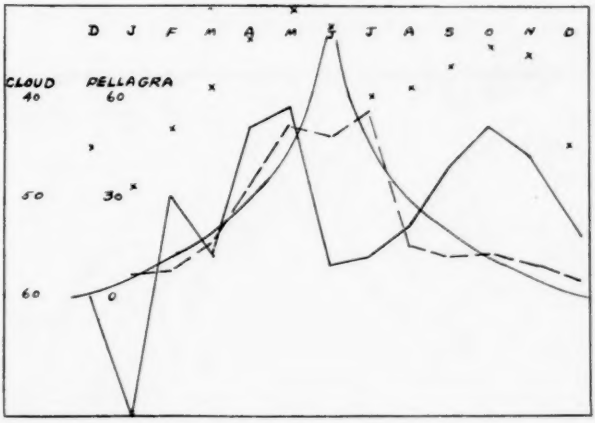


Chart 34.—Georgia, 1926.

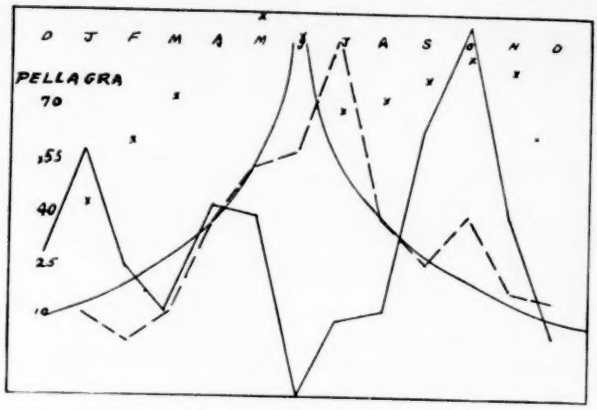


Chart 35.—Georgia, 1927.

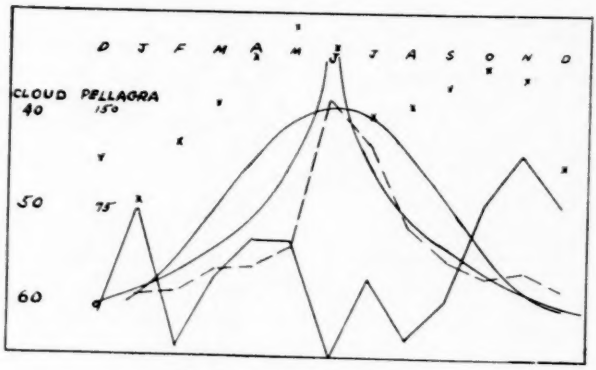


Chart 36.—Georgia, 1928.

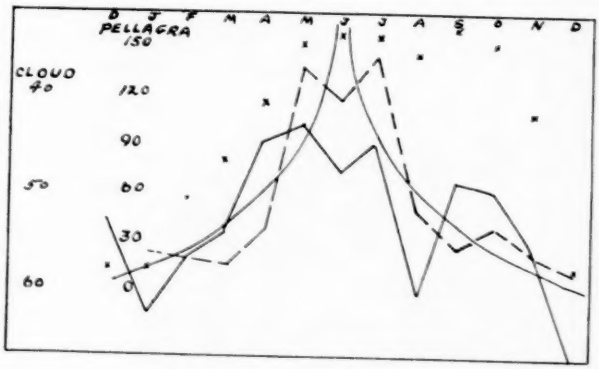


Chart 37.—Tennessee, 1926.

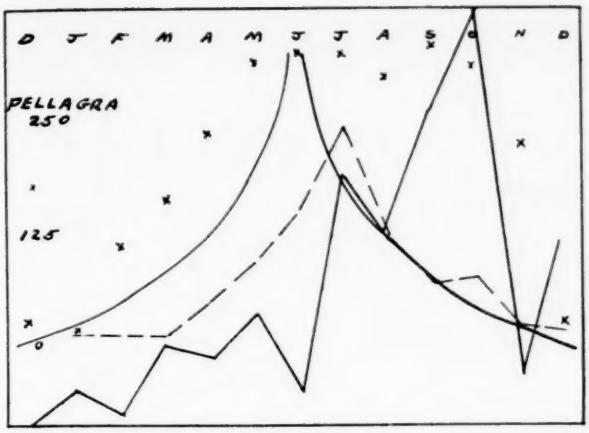


Chart 38.—Tennessee, 1927.

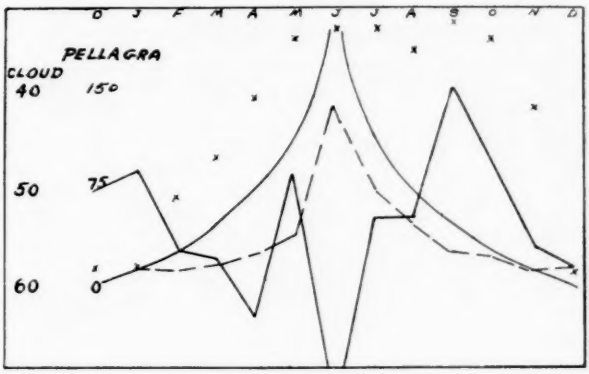


Chart 39.—Tennessee, 1928.

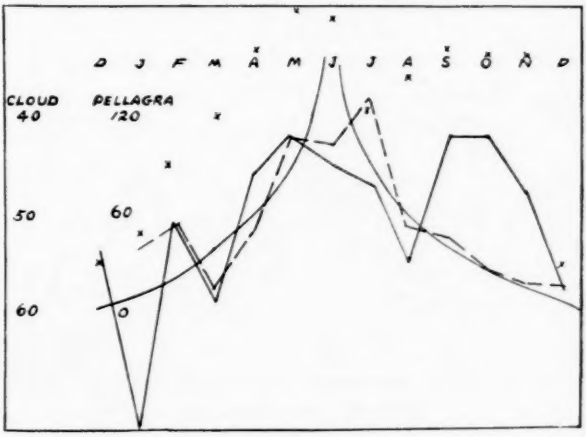


Chart 40.—Alabama, 1926.

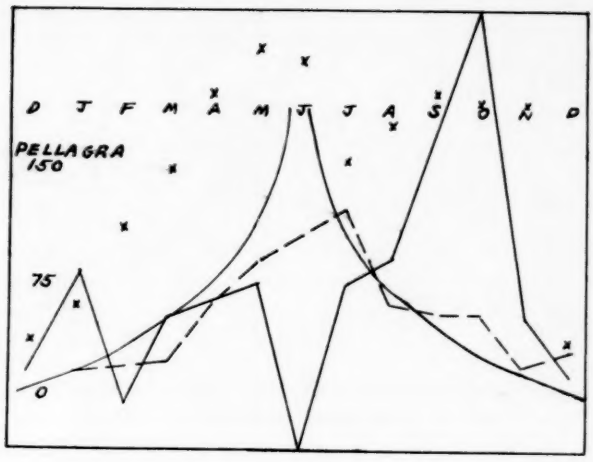


Chart 41.—Alabama, 1927.

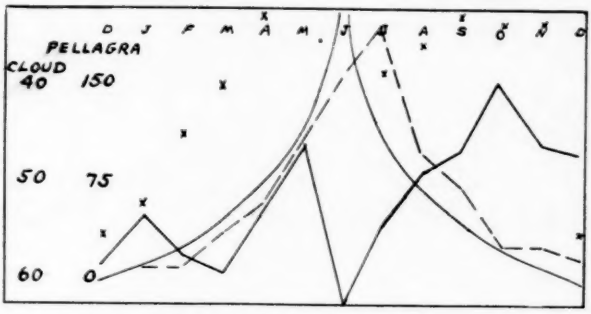


Chart 42.—Alabama, 1928.

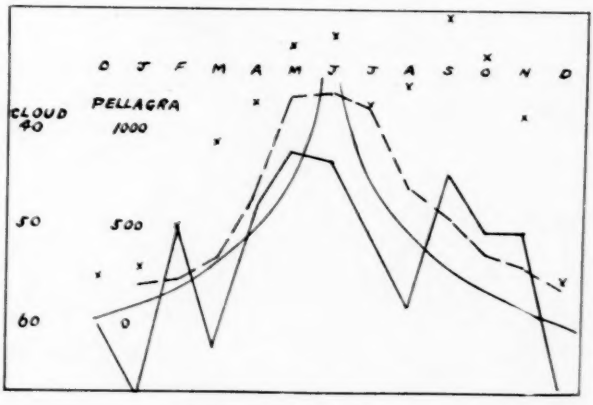


Chart 43.—Mississippi, 1926.

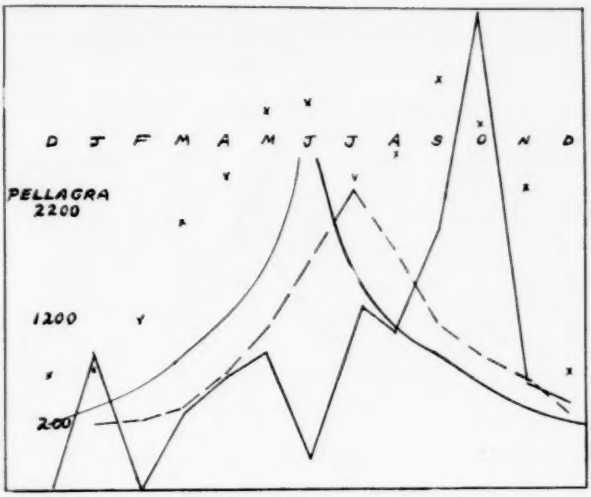


Chart 44.—Mississippi, 1927.

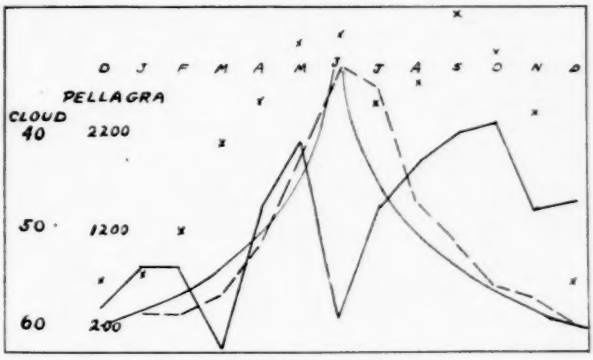


Chart 45.—Mississippi, 1928.

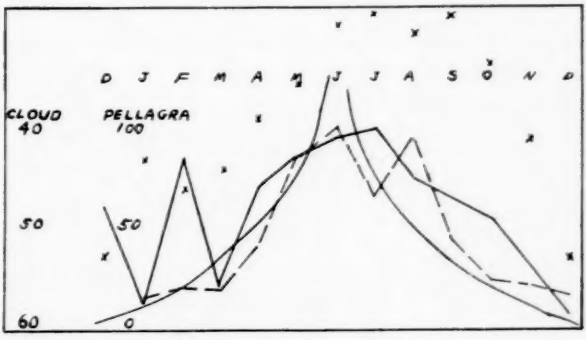


Chart 46.—Arkansas, 1926.

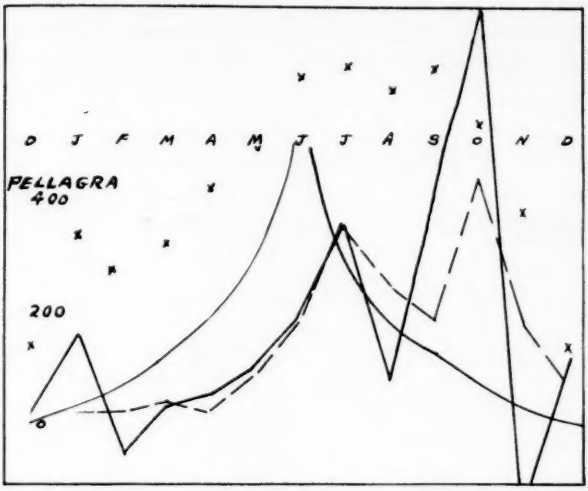


Chart 47.—Arkansas, 1927.

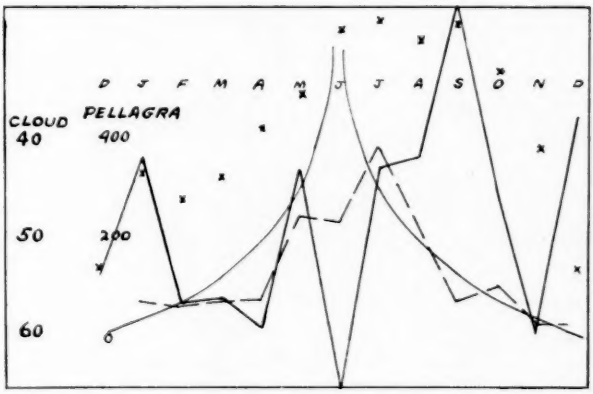


Chart 48.—Arkansas, 1928.

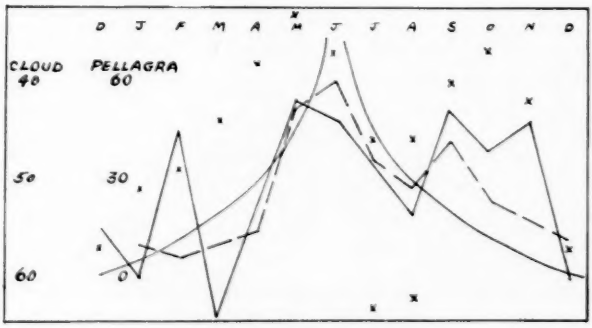


Chart 49.—Louisiana, 1926.

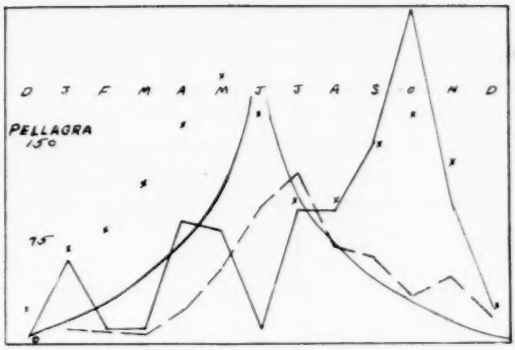


Chart 50.—Louisiana, 1927.

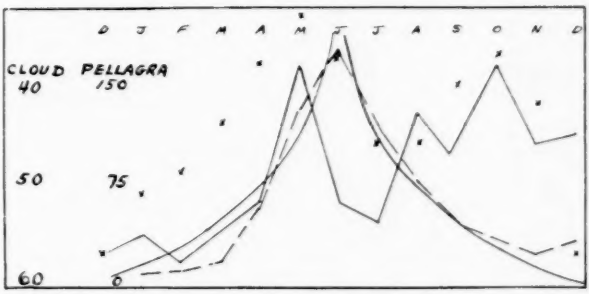


Chart 51.—Louisiana, 1928.

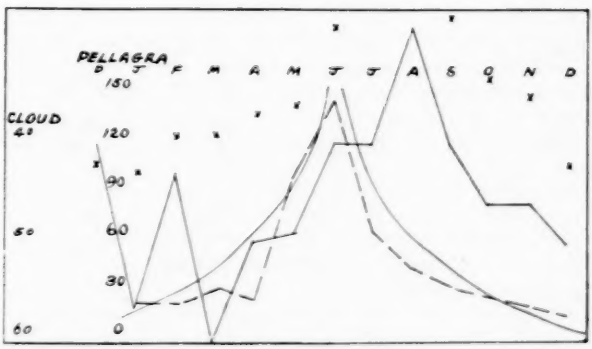


Chart 52.—Oklahoma, 1926.

ultraviolet radiation, or, if the curve tentatively presented as that of the average basal metabolism in Virginia is considered as applicable generally to the southern part of the United States, the tendency is for the seasonal incidence of pellagra to rise and fall in the direction opposite the rise and fall of the average basal metabolism.* The larger the number of cases of pellagra in a given state for a given year, the closer these parallels tend to be.†

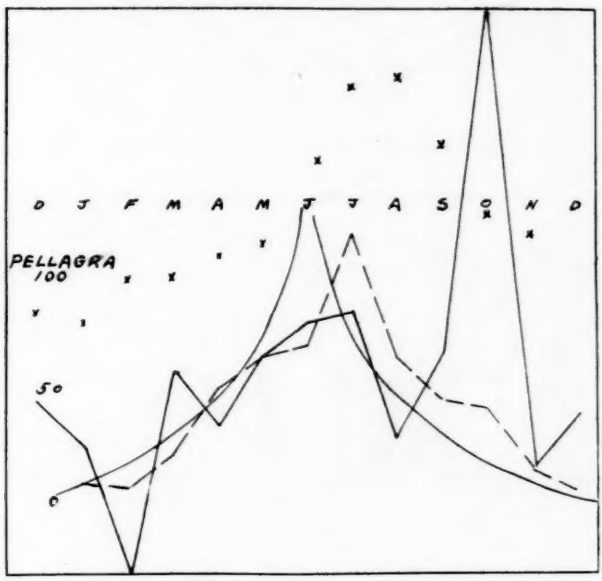


Chart 53.—Oklahoma, 1927.

Any comment on the seasonal character of pellagra should take into account the careful investigation of this and other features of the subject that has been made and published by the United States Public Health Service. In a study carried out in twenty-four cotton-mill

* A low average metabolic rate would appear to be less important in the etiology of pellagra than the relation of radiation during the winter to that during the summer; otherwise, there is reason to believe that pellagra would be more common in the tropics than in the southern part of the United States.

† The data for the incidence of pellagra were taken from the United States Public Health Reports. A few omissions were supplied by estimate. As a rule, the early months of the year appear to furnish a fairly reliable index to the total number of cases for the year.

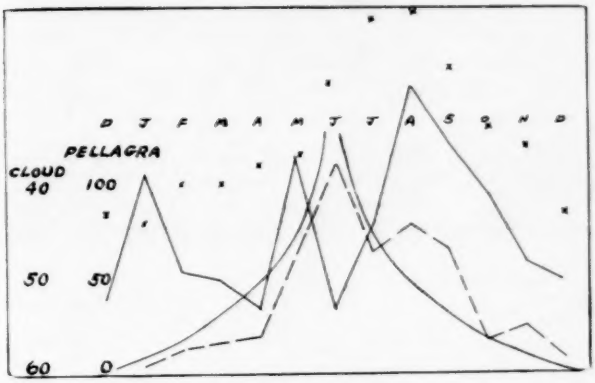


Chart 54.—Oklahoma, 1928.

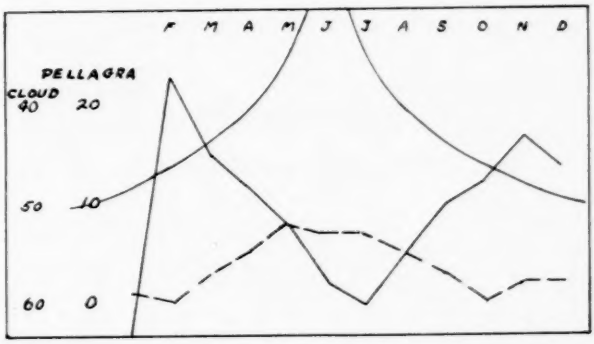


Chart 55.—Florida, 1926.

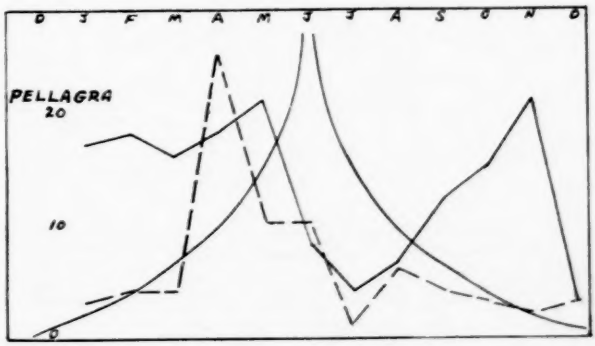


Chart 56.—Florida, 1927.

villages in South Carolina, from 1916 to 1921 [45]—which will be referred to hereafter as the Hygienic Laboratory report—the authors of this report stated that:

Our findings as they relate to the general curve of the seasonal incidence of the disease agree with those of the earlier students in the same locality, as they

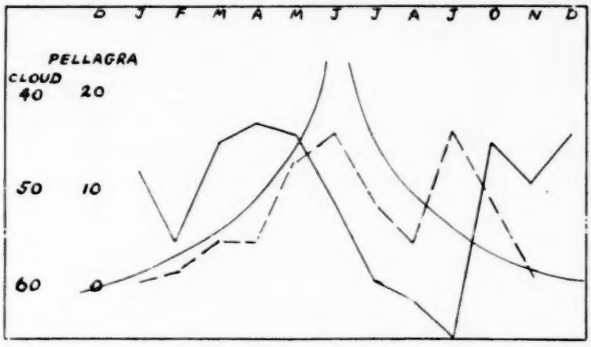


Chart 57.—Florida, 1928.

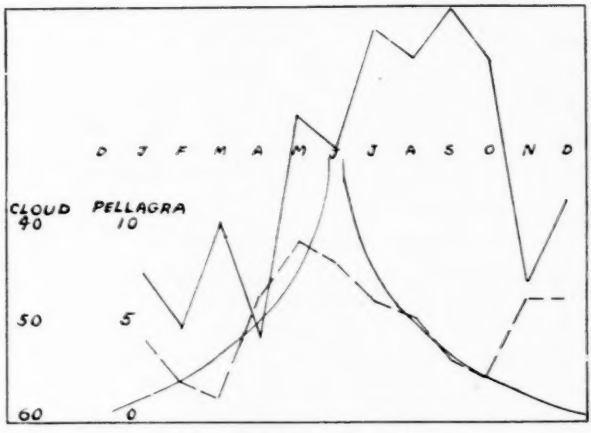


Chart 58.—California, 1926.

do also with the general experience of observers in other localities in the North Temperate Zone, both American and European (p. 33).

Chart 70 reproduces the curve representing the experience of these investigators, which they described as follows:

The incidence of the disease for the twenty-four villages may, therefore, be considered as describing a curve, the outstanding features of which would seem

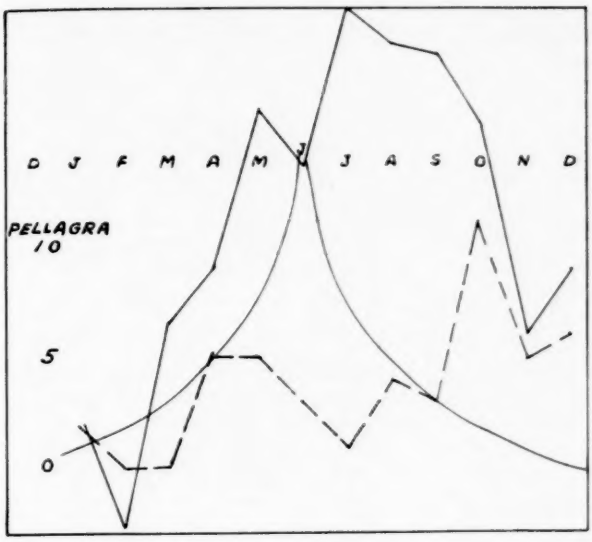


Chart 59.—California, 1927.

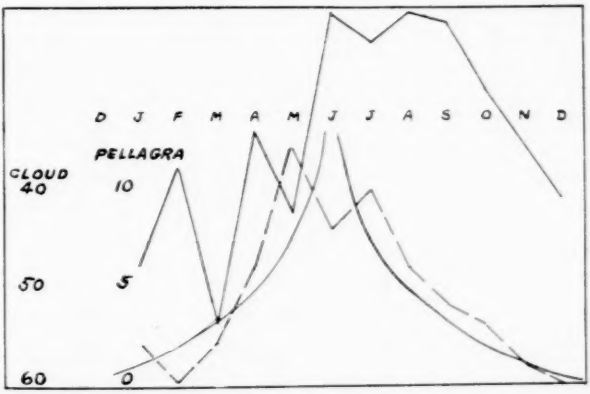


Chart 60.—California, 1928.

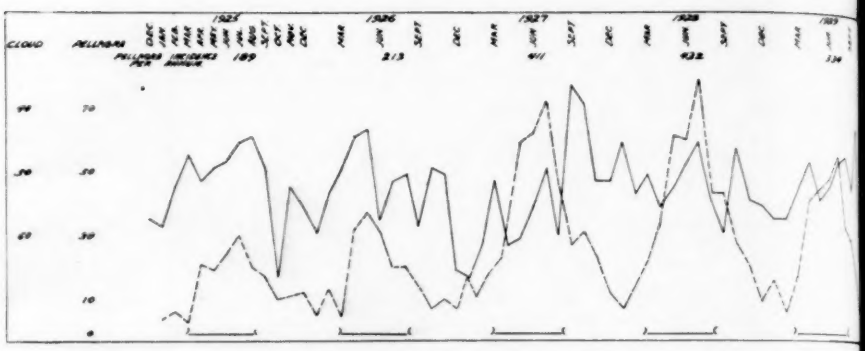


Chart 61.—Virginia, from 1925 to 1929, inclusive. The continuous line indicates the average cloudiness at all stations; the broken line, the monthly incidence of pellagra; the line in reverse parentheses, the summer season, the sun being north of the equator.

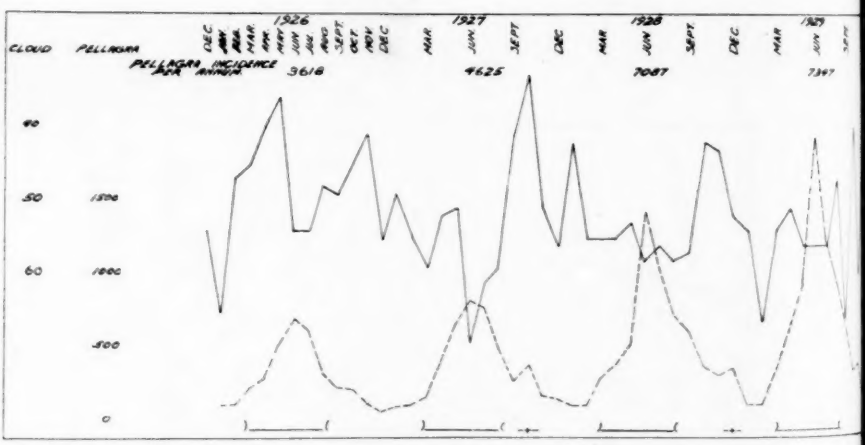


Chart 62.—South Carolina, from 1926 to 1929, inclusive. The continuous line indicates the average of cloudiness at all stations; the broken line, the monthly incidence of pellagra; the line in reversed parentheses, the summer season, the sun being north of the equator; the dash, plus, dash line, the secondary peak in the incidence of pellagra coincident with excess sunshine.

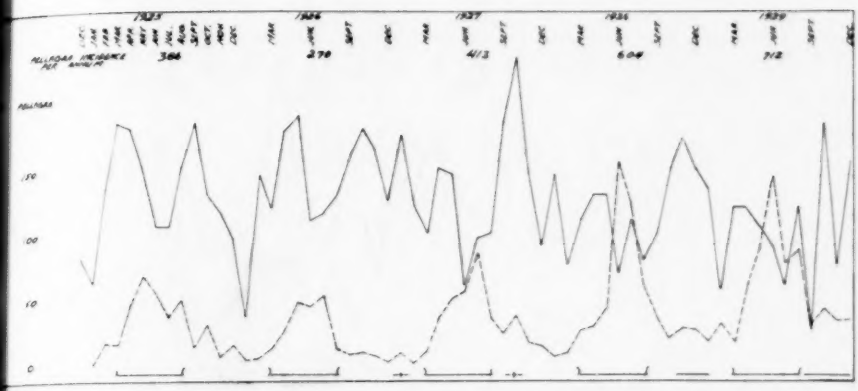


Chart 63.—Georgia, from 1925 to 1929, inclusive. The continuous line indicates the average of cloudiness at all stations; the broken line, the monthly incidence of pellagra; the line in reversed parentheses, the summer season, the sun being north of the equator; the dash, plus, dash line, the secondary peak in the incidence of pellagra coincident with excess sunshine.

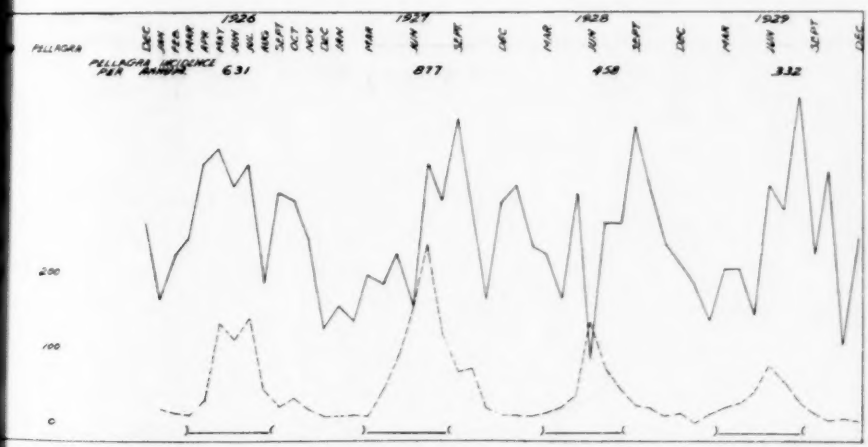


Chart 64.—Tennessee, from 1926 to 1929, inclusive. The continuous line indicates the average of cloudiness at all stations; the broken line, the monthly incidence of pellagra; the line in reversed parentheses, the summer season, the sun being north of the equator.

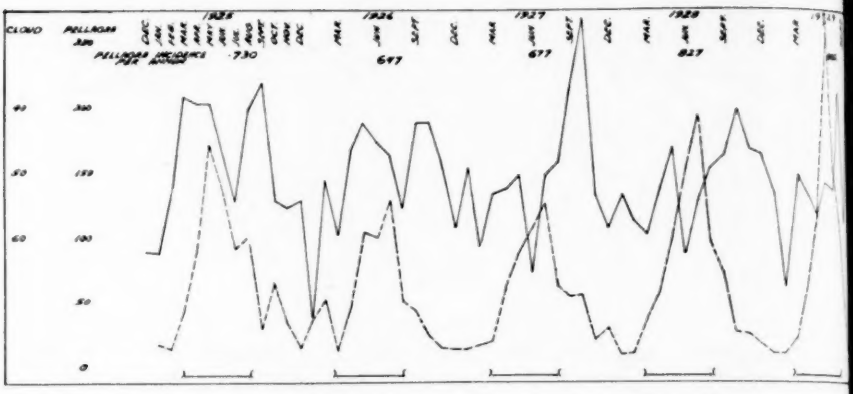


Chart 65.—Alabama, from 1925 to 1929, inclusive. The continuous line indicates the averag cloudiness at all stations; the broken line, the monthly incidence of pellagra; the line in reve parentheses, the summer season, the sun being north of the equator.

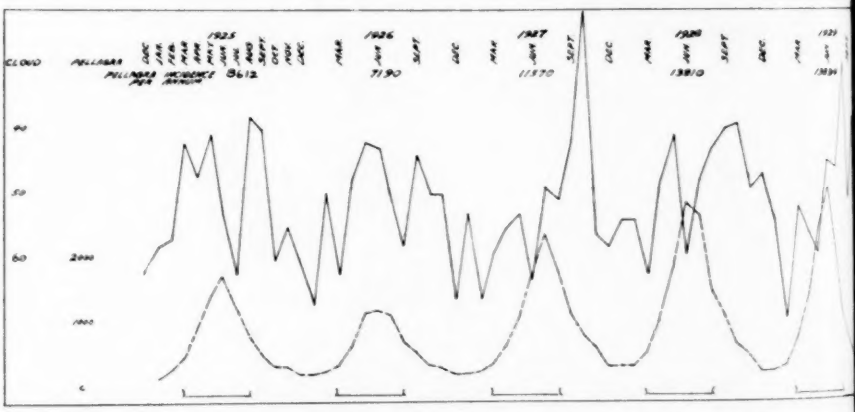


Chart 66.—Mississippi, from 1925 to 1929, inclusive. The continuous line indicates the aver of cloudiness at all stations; the broken line, the monthly incidence of pellagra; the line in reve parentheses, the summer season, the sun being north of the equator.

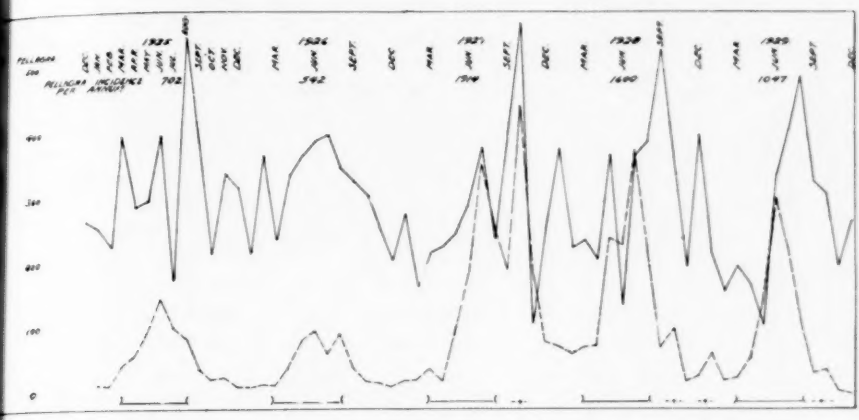


Chart 67.—Arkansas, from 1925 to 1929, inclusive. The continuous line indicates the average of udiness at all stations; the broken line, the monthly incidence of pellagra; the line in reversed rentheses, the summer season, the sun being north of the equator; the dash, plus, dash line, the ondary peak in the incidence of pellagra coincident with excess sunshine.

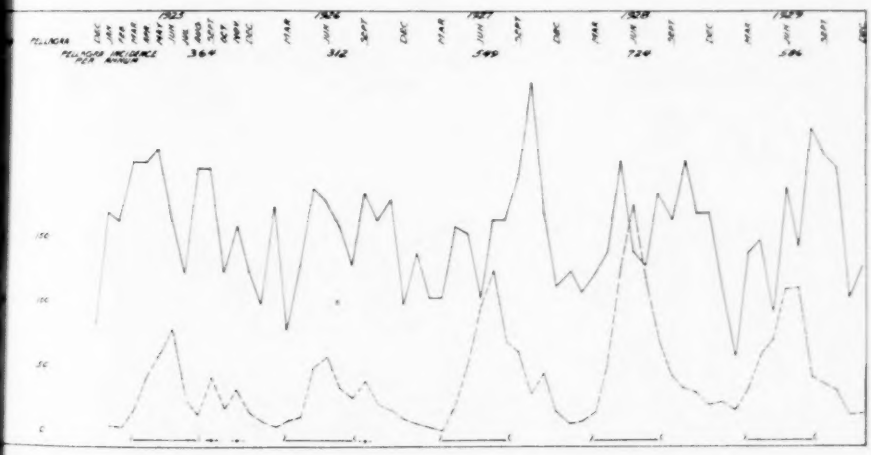


Chart 68.—Louisiana, from 1925 to 1929, inclusive. The continuous line indicates the average f cloudiness at all stations; the broken line, the monthly incidence of pellagra; the line in reversed arentheses, the summer season, the sun being north of the equator; the dash, plus dash line, the ondary peak in the incidence of pellagra coincident with excess sunshine.

to be its beginning with March, a steep rise during April and May to a sharp peak in the early part of June, followed by an even more precipitate fall beginning during the latter part of that month, continued through July and August, and the termination with September or during October.

Continuing the discussion,[45] these authors stated:

The extraordinarily marked seasonal character of the endemic disease would therefore seem to be a phenomenon related to an annually recurring factor or factors operating within wide geographical limits. In view of the proven dietary relation of the disease, it may be suggested that this annually recurring factor is probably the recurring variation in diet brought about by a seasonal modification of food supply which, in its turn, is probably the result of a variable complex of climatic and economic factors (p. 33).

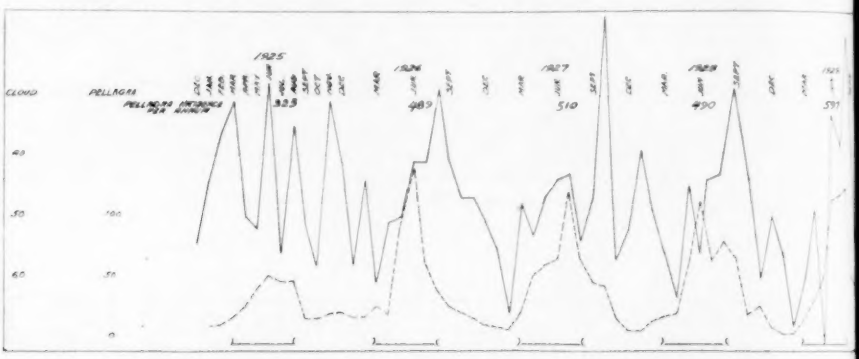


Chart 69.—Oklahoma, from 1925 to 1929, inclusive. The continuous line indicates the cloudiness at Oklahoma City; the broken line, the monthly incidence of pellagra; the line in reversed parentheses, the summer season, the sun being north of the equator.

The curves shown in charts 28 to 69 are therefore no exception to the general experience, and the fairly close parallel between the curves for the incidence of pellagra and for the air filter would suggest that the "annually recurring factor" is directly, and not indirectly, "climatic" and is not represented by a "recurring variation in diet" resulting from a variable complex.

In a further discussion of the general curve of incidence, the investigators from the Hygienic Laboratory stated:

Recurring variation in diet would explain the first part, the rise and upward course, of the curve of incidence as coming late in or immediately after, and due to a defective dietary period in the later part of the winter and of the early spring. It would explain the decline and cessation of incident cases as due to favorable modifications in diet associated with and following the changes in the food supply of the later part of the curve of seasonal incidence.

In a footnote, it is observed "there are reports in the literature which would indicate that in some localities the curve of incidence may or has shown a second and much less marked peak in the late summer. This would appear to depend on factors of a less general character" (p. 33). From an examination of charts 28 to 69, it would seem that this statement might be broadened to say that such a second and no less marked peak (chart 47, Arkansas, 1927) may occur as late as October.

According to charts 28 to 69, the peak of the incidence of pellagra is near the summer solstice. A secondary rise or peak following the summer solstice is not seen,* except when there is a corresponding absence of cloudiness or a relative rise in the percentage of sunshine. In general, the curve for pellagra deviates from that for the air filter to correspond with excess sunshine (charts 32, 35, 37, 38, 41, 47, 50, 54,

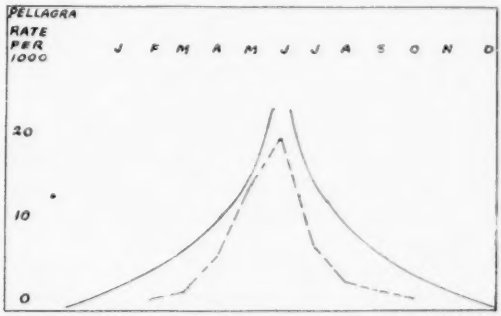


Chart 70.—The broken line indicates the monthly incidence of pellagra in twenty-four villages of South Carolina in 1917. (From Hygienic Lab. Bull., no. 153.)

62, 63, 67 and 68). Doubtless, as many persons have a tissue metabolism favorable to the development of pellagra in August as in either July or September, but they lack whatever influence there may be in a relatively greater solar radiation or irradiation.† A limitation in intensity in solar radiation in the autumn is imposed by the declining angle of the sun's rays, apparently reflected in the autumnal incidence of pellagra both in cotton-mill workers and in the rural population. The almost complete cessation of the incidence of pellagra in the cotton-

* Arkansas, 1926 (chart 46), is an exception, but the seasonal curve of the percentage of cloud also appears to be exceptional. There is also the possibility that a particular explanation is applicable, as in the instance of August, 1921, in Arkansas.

† There is a tendency among farmers who raise cotton to "ease off" in attention to the crop in August (Vance, reference 110).

mill villages during the late fall and winter months and the continuation of a relatively low but definite incidence in rural populations suggest a positive influence of exposure to the sun's rays in the latter group. (The autumn peak in sunshine apparently must have both height and breadth in order to effect an autumn rise in pellagra.)

In the Hygienic Laboratory report careful attention is given the "peak month" in the various villages studied, and on the basis of the chronological position of the peak of incidence, the villages fall into three groups.[45] The authors noted:

> As is clearly evident, the outstanding differences in seasonal distribution of "onset" relate practically altogether to the position of the peak, so that it would seem as if the factor or factors responsible for the development of the disease, although beginning to make themselves felt at about the same time in all three groups of villages, for some reason attained maximum force or began to be exhausted or both approximately a month sooner in the villages of two of the groups than in those of the third (p. 28).

Reference to charts 28 to 69, as stated, shows that the peak of the incidence of pellagra occurs near the summer solstice. It may follow the summer solstice or it may precede it, but as far as the observations go, it does not precede the peak of sunshine or the absence of cloudiness so far as this peak occurs prior to the summer solstice. If the peak of sunshine is reached in May or June, the peak of pellagra is reached in June; if the peak of sunshine is delayed till July, the peak of pellagra is delayed till July.

In regard to the question of the chronological position of the peaks in the villages mentioned in the Hygienic Laboratory report, it is interesting to compare, so far as the available data will permit, the chronological peak of the incidence of pellagra with the chronological peak of sunshine. United States Weather Bureau stations are located at Greenville and at Columbia. Since the location of the villages may be identified in the Hygienic Laboratory report (chart 91), they may be grouped with reference to their proximity to Greenville and Columbia, respectively, and the prevailing conditions of the weather as reported for these stations, respectively, may be used as the nearest available approximation to the conditions of the weather that prevailed in the groups of villages at the time studied.

For one village with a population of 803 in the Greenville area, the Hygienic Laboratory report gives data on the incidence of pellagra for five years, from 1917 to 1921 (charts 71, 72, 73, 74 and 75). For two villages (Gy and Ola) in the Columbia area (chart 76), data are published for 1917. For five villages (Dun, Jn, Fn, Gr and Vr) in Greenville County data on the weather may be considered to have been fairly certainly represented by the United States Weather Bureau

report for Greenville, and data on pellagra are available for 1917 (chart 77). Table 13 of the Hygienic Laboratory report enables a comparison with available data on the weather of the seasonal incidence and seasonal prevalence of pellagra in 1918 for six villages in the Green-

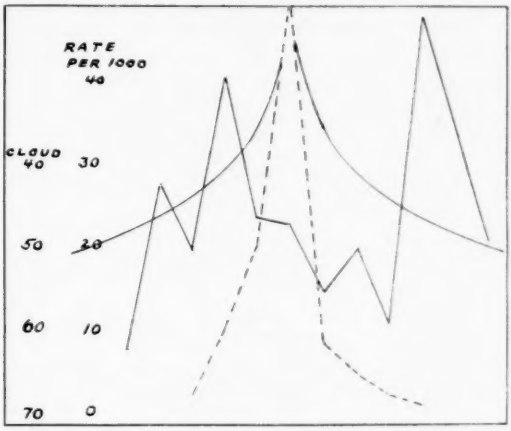


Chart 71.—The continuous line indicates the average cloudiness at Greenville in 1917; the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1917.

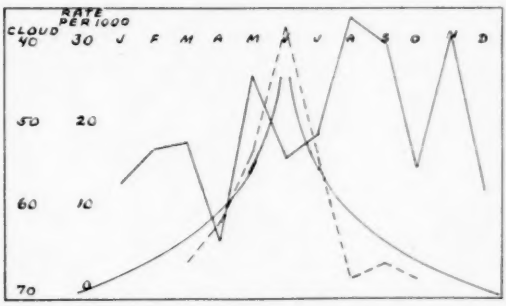


Chart 72.—The continuous line indicates the average cloudiness at Greenville in 1918; the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1918.

ville area (chart 78). The incidence of pellagra in 1917 for seventeen villages in the area of Greenville, though not in Greenville County, and condition of the weather prevailing in Greenville at that time are represented in chart 79.

Examination of these charts shows no tendency for the peak of pellagra to precede the peak of sunshine. The peak of pellagra is more prone to fall in June and that of sunshine in April (charts 71, 76, 77 and 79). At In, in 1920 (Hygienic Laboratory report,[45] table 33), there were 5 cases in May and only 4 in June, though the percentage

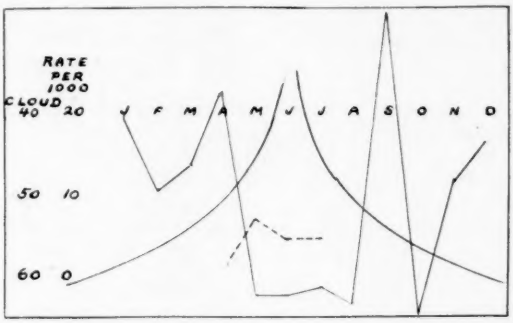


Chart 73.—The continuous line indicates the average cloudiness at Greenville in 1919; the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1919.

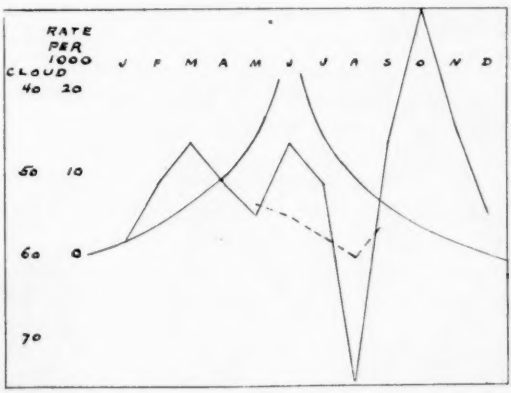


Chart 74.—The continuous line indicates the average cloudiness at Greenville in 1920; the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1920.

of sunshine in June was slightly higher than that in May, but the sunshine of March equaled that of June (chart 74); this is obviously negligible. When the peak of pellagra occurred in May (charts 73, 74 and 75), the peak of sunshine occurred in April or March.

The clinical progress of the disease is generally similar to the curve of incidence—spring onset, summer exacerbation and improvement in the fall and winter. Any study of the clinical state, metabolism or effect of therapy should therefore take into account the season. Sullivan, Stanton and Dawson's [97] observations covered the period from July 13 to Oct. 11, 1917.

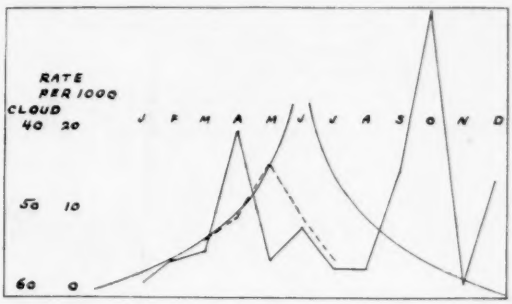


Chart 75.—The continuous line indicates the average cloudiness at Greenville in 1921; the broken line, the monthly incidence of pellagra in one village in the area of Greenville in 1921.

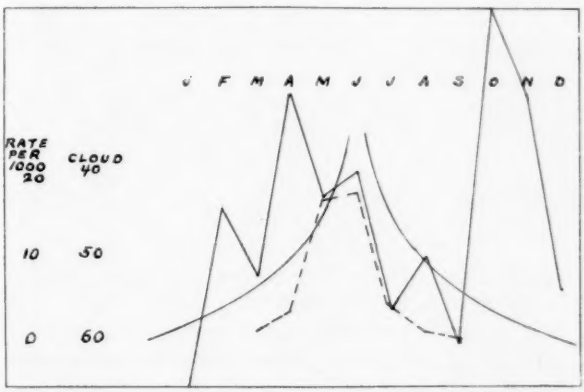


Chart 76.—The continuous line indicates the average cloudiness at Columbia in 1917; the broken line, the monthly incidence of pellagra in two villages in the area of Columbia in 1917.

The investigators from the Hygienic Laboratory found that the seasonal prevalence differed from the seasonal incidence only in a lag of time of about two weeks. They stated:

This brings out concretely what has long been recognized clinically, namely, that cases of pellagra "normally" tend to get well in the fall with the advent of

cool weather. This old and very striking clinical observation gave rise to the idea that in some way the cooler temperature in itself had a beneficial effect. In reality, however, the decline in the season of prevalence, even allowing for the limitations of our data, sets in before the advent of cool weather, so that this can hardly be the real explanation of the phenomenon. The similarity of the curve of prevalence to that of incidence naturally suggests that the factors, or some of them, operating to limit the season of incidence also operate to cut short the attack.

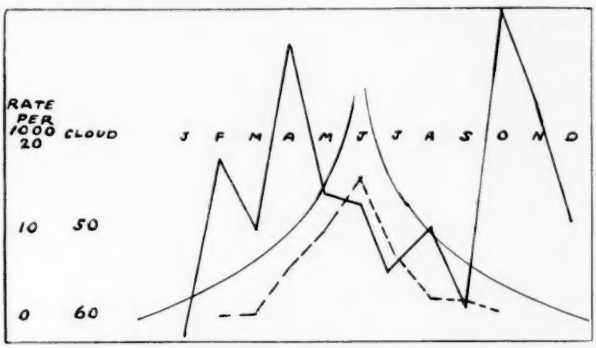


Chart 77.—The continuous line indicates the average cloudiness at Greenville in 1917; the broken line, the monthly incidence of pellagra in five villages in Greenville County, 1917.

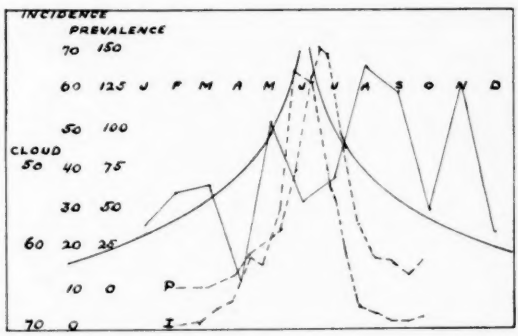


Chart 78.—The continuous line indicates the average cloudiness at Greenville in 1918; curve *I*, the incidence of pellagra in 1918; *P*, the prevalence of pellagra in 1918, in six villages in the area of Greenville.

Here again there appears to be another set of parallels to the curve of the air filter and possibly that of the basal metabolism reversed, culminating in the "normal" tendency to get well in the fall. Though the decline of the season of prevalence sets in before the advent of cool weather, it does not set in before the advent of a decline of the sun toward the south.

That the investigators from the Hygienic Laboratory did not consider the matter closed with their report is shown by the following discussion:

> Of the factors suggested as probably concerned in cutting short the season of incidence, the normal seasonal modification in food supply occurring in the summer would seem to be the only one that reasonably can be suggested as capable of operating in such a way as to limit the duration of the attack—that is, of prevalence. *A priori*, this factor would seem entirely adequate to explain the normally self-limiting character of the attack. But whether it actually operates in the manner here suggested, as seems to us most probable, or whether some other factor or factors alone or in cooperation with the seasonal modification in diet are concerned in the explanation of the phenomenon under consideration remain for further study to determine.

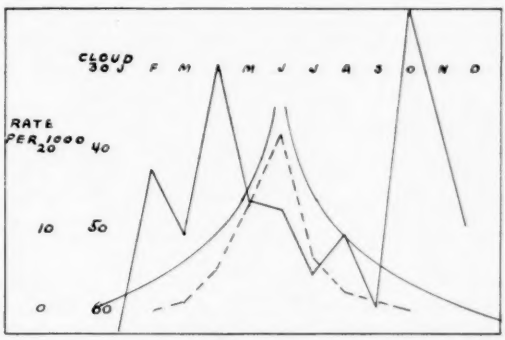


Chart 79.—The continuous line indicates the average cloudiness in Greenville in 1917; the broken line, the monthly incidence of pellagra in seventeen villages in the area of Greenville in 1917.

VARIATIONS IN THE ANNUAL INCIDENCE OF PELLAGRA WITHIN THE PELLAGRA BELT

In the foregoing discussion of the seasonal incidence of pellagra, the positive influence of varying intensities of sunlight has been considered, without reference to the principle suggested by Laurens as to the effect of deviation from the usual radiant energy. Certain features of pellagra will be considered, with the idea in mind of a positive effect of the ratio between exposure to the solar rays in winter and summer. Stated differently, the tentative assumption is that the solar radiation available in winter by reason of an absence of cloudiness constitutes for the population concerned a standard of "usual radiant energy" which acts as a unit of exposure to which the population has for the time being become accustomed, and deviation from which as the sun approaches the summer solstice tends to produce pellagra. If the intensity of the

summer rays is considered as constant by ignoring summer cloudiness,* increased cloudiness in winter and increased exposure to solar rays in summer, as in the planting of certain crops, would tend to have a positive pellagra-producing effect.

The state (and sometimes the county) is the available unit for data concerning the incidence of pellagra. Variations in the annual incidence will therefore be considered with reference to these units, and the apparent influence of the factors winter cloudiness and the planting of crops, together with a factor to be defined later as the delayed incidence or momentum, will be examined.

First, however, reference will be made to the relationship between winter cloudiness and the average basal metabolism in a limited set of observations (table 19).

TABLE 19.—*Observations at Richmond, Va.*

	1927	1928
Low basal metabolic rate for the year	(July) —10.8	(Sept.) —8.49
Average for summer months:		
June	— 6.88	—7.95
July	—10.80	—5.57
August	— 7.46	—2.20
Average	— 8.38	—5.24
Winter cloud	62	46

The ratios derived from table 19 show, if anything, a depressant effect of increased winter cloudiness (1927) on the average basal metabolism for the following summer months.

Chart 80 shows the ratio of the winter cloudiness of 1928 to that of 1927, and the ratio of the pellagra in 1928 to that in 1927 for the states in which pellagra is reportable. Georgia was the only state in which the winter cloudiness of 1928 exceeded that of 1927, but in six states (Virginia, Mississippi, South Carolina, Alabama, Louisiana and Georgia) the ratio of the incidence of pellagra was greater than 1. It follows, therefore, that in general there was a greater incidence of pellagra in 1928 than in 1927, in spite of a generally clearer winter. This general tendency will be referred to later in connection with the delayed onset or momentum. For the present, it is noted that Tennessee, the

* By reason of the lack of solar radiation, a sensitizing feature may well be more significant than the intensity of the summer rays. The mass of the atmospheric filter is not greatly influenced by the angle at the sun's maximum altitude at 40° and 34° latitude, respectively (1.3 miles), but is greatly influenced by the minimal seasonal angle at these latitudes, respectively (18.85 miles). There seems to be little difference between the sun's erythematous power as measured by the air mass penetrated, at Philadelphia (40°) and Wilmington, N. C. (34°), but at Wilmington (34°) and Tampa (28°) there is a difference of 11.3 miles (93.2 miles less 81.9 miles).

state with the lowest ratio of winter cloudiness, did not show an increase, but a fall, in the incidence of pellagra, and that of the four states with the lowest ratio of winter cloudiness (Tennessee, Oklahoma, Virginia and Arkansas), none showed an increase and all, except Virginia, showed a decrease of pellagra in 1928 as compared with 1927.

With reference to Virginia, in chart 81 it is obvious that while all sections of the state showed approximately the same decreased ratio of 1928 to 1927 winter cloudiness, the rise in the incidence of pellagra was limited to two sections in which 95.4 per cent of the tobacco crop was planted, that these sections showed an increase in the planting of

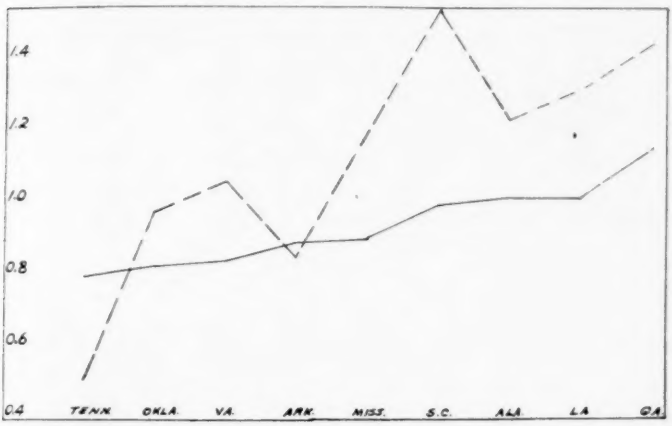


Chart 80.—Nine states. The continuous line indicates the ratio of winter cloudiness, 1928:1927; the broken line, the ratio of the incidence of pellagra, 1928:1927.

tobacco in 1928, and that the increase in pellagra in these sections, respectively, was proportional to the increase in the planting of tobacco.

Charts 25 and 82 show the distribution of pellagra and the distribution of tobacco and cotton acreage, respectively, in Virginia in 1927. Wise County (in the southwest) is relatively densely populated and is strikingly low as compared with the other counties of Virginia in the ratio of food and feed raised to the needs of the population.[48]

The remaining five states shown in chart 80 (Mississippi, South Carolina, Alabama, Louisiana and Georgia) showed increased ratios of pellagra in general agreement (except for South Carolina) with the relatively increasing ratios of winter cloudiness. The significance of these comparisons will possibly be increased in view of further analysis to be made of the factors under consideration.

Chart 24 suggests that unusual conditions of the weather, such as the cloudiness in February, 1927, over the area of the southern part of the United States generally, may have peculiar significance. The correlation between the winter cloudiness for 1926 and 1927 and pellagra for these two years is less close than the correlation between the cloudiness in February and pellagra for the same periods.

The predominantly rural character of pellagra (chart 126) suggests that if the duration of exposure to solar rays of relatively high intensity is a factor in the etiology of the disease, the planting of cotton and tobacco is of especial interest, because of their importance as major crops in the pellagra belt and because the crops are planted in a relatively

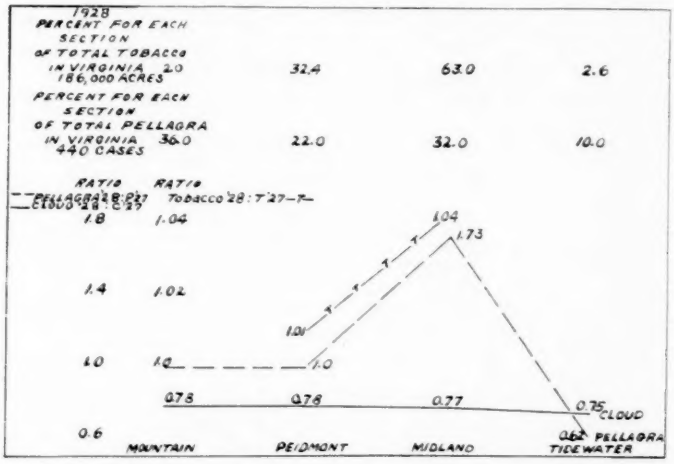


Chart 81.—Virginia. The continuous line indicates the ratio of winter cloudiness, 1928: 1927; the broken line, the ratio of the incidence of pellagra, 1928: 1927; the dash *T* line, the ratio of tobacco acreage, 1928: 1927.

great intensity of solar rays (near the summer solstice).* However, it should also be noted that these crops probably represent the extreme of the tenantry (economic) factor emphasized by Goldberger and his associates.

If the number of persons required to plant an acre of cotton (one person to five or six acres—Vance), the intensity of the solar rays during the planting of cotton and the dietary characteristics of the popu-

* For comparison with the time of planting these crops in North Carolina with the time of planting and harvesting other crops, reference should be made to the Farm Forecaster, North Carolina, 1928-1929, p. 26, and to Phillips (reference 78).

lation planting the cotton are taken as constant, an acre of cotton may be considered a unit of pellagra-producing factors, as is shown roughly for Mississippi in charts 96 to 101, and a comparison of the incidence of pellagra in relation to the exposure during the previous winter may be regarded as an experiment on a grand scale, the individual characteristics of metabolism being taken care of in an average of the large number of persons employed.

Delayed Incidence or Momentum.—Whatever the conditions favorable to a high incidence of pellagra may be, it seems reasonable to assume that conditions operating broadly to produce a high incidence in any given year would tend to affect an indefinite number of persons

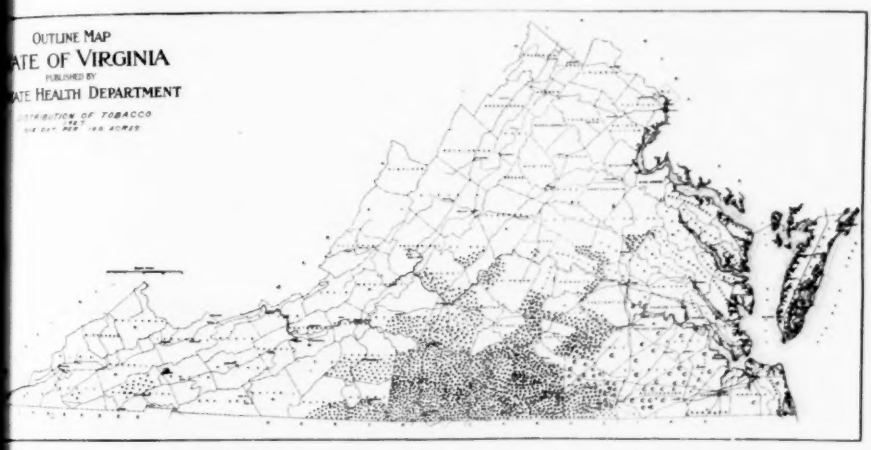


Chart 82.—Virginia, 1927. The dots show the distribution of tobacco acreage (divided by 100); *c* shows the distribution of cotton acreage (divided by 1,000).

who, whether the disease did or did not develop in them during the current year, would be somewhat more liable to the disease the following year than would have been the case had the conditions of the current year been less favorable to a high incidence. In other words, an increased incidence, for example, in 1927 as compared with that in 1926, might be expected to tend to an increase in 1928 in the absence of a definite reduction in the pellagra-producing factors. This assumed tendency may be referred to as a delayed incidence or momentum.

The relative incidence in 1927 was actually and generally high in comparison with that in 1926 (chart 24), and thus conditions favorable to the further increase in 1928 were probably created. Such may also be the significance of the observation of the Hygienic Laboratory,[45] that "recurrent attacks probably tend to appear somewhat earlier in the

year than do initial attacks" (p. 33). However, if the supposed "delayed incidence" is real, the data point to the fact that the delay and the subsequent development of the disease are limited and defined by the same curve as the incidence of new cases as a whole and of recurrent cases, namely, the curve of the air filter.

It is hardly open to question that any tendency to error through the listing of recurrent cases as new cases would tend to be exaggerated by a high incidence during the previous year and thus add to a seeming momentum.

The idea of a delayed incidence may be illustrated by the fact that a seed that is sown one year may spring up the following year. Wood [120] referred to pre-pellagrous symptoms that made their first appearance about Christmas time, suggesting a premonitory hint of a delayed incidence.

The investigators from the Hygienic Laboratory [45] referred to a possible "exhaustion of the human material of pellagrous potentiality"

TABLE 20.—*Mississippi*

	Jan.	Feb.	March	April	May	Total	Nov.	Dec.
1926	210	245	353	652	1,178	7,150	314	213
1927	217	257	394	685	1,100*	11,570	638†	313†
1928	355†	349†	549	1,029	1,865	13,810	514	279

* Estimated.
† There was not an indication of "exhaustion of human material," but an indication of susceptibility of population and increased potentiality for the succeeding year.

(p. 34). It is possible that Washington County, Mississippi, represents an instance of this exhaustion (see table 21). The notion involved in "delayed incidence" is the opposite. It does not seem inherently contradictory to suppose that high sunshine in the winter might result in an increased incidence of pellagra during the winter months and at the same time tend to offset the development of the disease during the following summer.

The tendency to a delayed incidence may be illustrated in the figures given in table 20 for Mississippi.

Statistically, there is a valid objection to considering along with supposed etiologic factors one expression of the incidence of pellagra, when the effect under consideration is another expression of this incidence. This objection is regarded as somewhat less valid in view of the tendency for the incidence of pellagra to approach zero in the winter.

In North Carolina, pellagra was not made a reportable disease until 1929; however, the curve of the death rate in the state for several years is shown in chart 83. There is a decidedly upward trend after 1923. The trend of the curve representing winter cloudiness, cotton and

tobacco, when reduced to a common scale, is also upward until 1927 (chart 84). In 1927, the death rate for pellagra showed a further rise, though there was a sharp reduction in the planting of cotton. Winter cloudiness and the planting of tobacco, however, were in excess in 1926. In 1928, the death rate for pellagra still further increased; cotton and tobacco acreage increased over that of 1927, but the winter cloudiness showed a sharp decline. It is possible that the increased death rate for pellagra reflected the history of pellagra of the preceding several years (momentum). Further data are necessary before the relative influence of pellagra-producing and pellagra-reducing factors can be appraised. The scales used in chart 84 are purely arbitrary and do not furnish a basis for a comparison of values, except in trends.

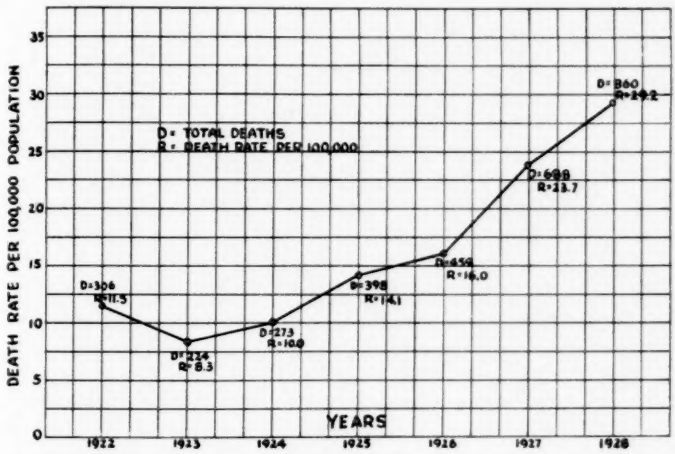


Chart 83.—Death rates from pellagra in North Carolina, from 1922 to 1928. (From the North Carolina State Board of Health.)

If in any year in any state an increased incidence of pellagra (assuming reliable data) and a decline in winter cloudiness, cotton, tobacco and momentum are noted, it is obvious that the etiologic factors of pellagra are not comprehended in these influences. However, the evidence that has been adduced by Goldberger and others in favor of a deficiency of food and an economic cause of pellagra has been employed by them with scientific caution as explanatory of certain features of the incidence of the disease (Hygienic Laboratory Bulletin,[45] pp. 45-64) and obviously is available for consideration in connection with any other supposed etiologic factor. These authors [45] stated that:

It seems reasonable to infer, therefore, that the year-to-year fluctuations in pellagra incidence in endemic localities are bound up with year-to-year fluctuations

in economic conditions—that is, with conditions that influence the ability of a certain section of the population to procure an adequate diet, particularly at a certain season, the late winter and early spring of the year. We believe we have here in a concrete, definite and scientific form, based on intensive study, the explanation, or a very important part of the explanation, of the long recognized phenomenon of year-to-year fluctuations in incidence of endemic pellagra (p. 60).*

Charts 85, 86 and 87 show the distribution of deaths from pellagra and of cotton and tobacco acreage, respectively, in North Carolina in 1928. For comparison, charts 88, 89 and 90 show the distribution of other major crops in this state in the same year.

Charts 91 and 92 show the distribution of pellagra and of cotton and tobacco acreage, respectively, in South Carolina for 1927. Chart

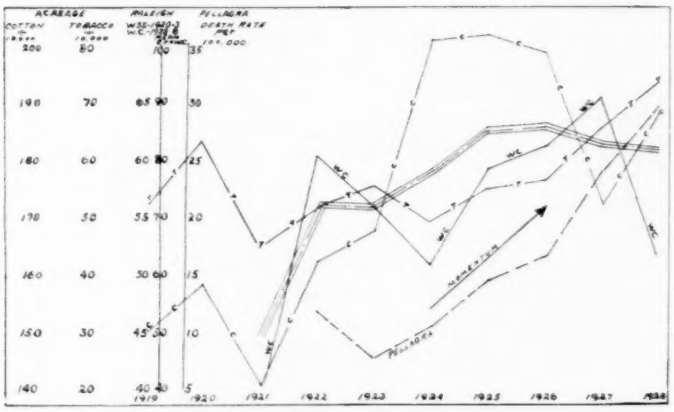


Chart 84.—North Carolina. Curve *c* indicates the cotton acreage; curve *T*, the tobacco acreage, and curve *WC*, the winter sunshine from 1921 to 1923, and winter cloudiness, from 1924 to 1928, at Raleigh. The triple line indicates the mean cotton acreage, tobacco acreage and winter cloudiness; the broken line, the death rate from pellagra per hundred thousand.

91 also shows the approximate location of the twenty-four villages studied in the Hygienic Laboratory report.

* Though not necessarily a contradiction, it is nevertheless difficult to apply this principle to the decrease in pellagra in certain European countries following the World War. In the League of Nations Health Reports a statement is made to the effect that the decrease in pellagra in Roumania after the war was expected to be permanent, but it was found otherwise. In contrast is McCollum's statement: "Marked deficiency of protein in the diet over a considerable period, as when the population is at war or approaching famine conditions, and is forced to subsist on a diet of cabbage, lettuce and other green foods, has been observed to cause endemic dropsy" (reference 72). This, however, is not the deficiency described by Goldberger.

The annual incidence of pellagra in 1926, 1927 and 1928, in Arkansas and Mississippi, is of special interest. The incidence will be considered in connection with the data available for each, which differ in some respects.

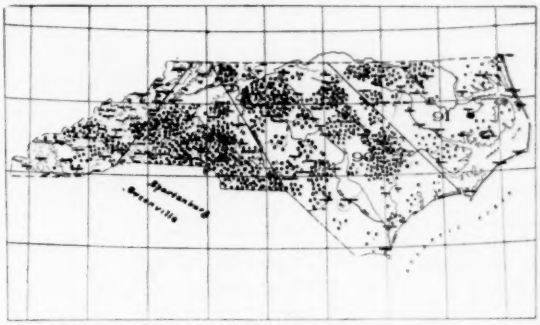


Chart 85.—Distribution of deaths from pellagra in North Carolina in 1928. (From the North Carolina State Board of Health.)

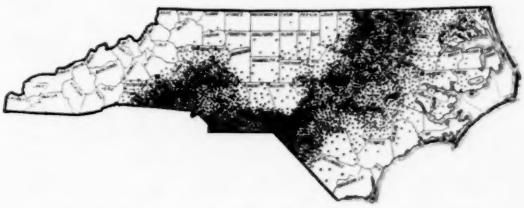


Chart 86.—North Carolina, 1928. Distribution of the cotton acreage. The value of the 1928 crop of cotton lint is represented by one dot to each $25,000.

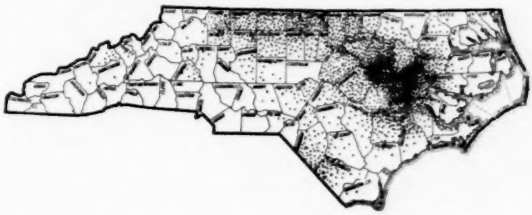


Chart 87.—North Carolina, 1928. Distribution of the tobacco acreage. The value of the 1928 crop of tobacco is represented by one dot to each $50,000.

In Arkansas, in each of the three sections of the state, western, middle and eastern (charts 93, 94 and 95), the winter cloudiness of 1927 exceeded that of 1926 and 1928, and conversely the cotton acreage was

reduced in 1927.[4] The net result apparently attributable to these factors was a rise in the incidence of pellagra in 1927 above that of 1926 or 1928, roughly in proportion to the excess of winter cloudiness. If the increased incidence of pellagra in 1927 is considered as a factor of momentum resulting in a delayed incidence, its effect is seen in the failure

Chart 88.—North Carolina, 1928. Distribution of the corn acreage. The value of the 1928 crop of corn (grain) is represented by one dot to each $10,000.

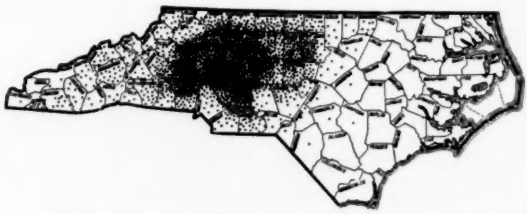


Chart 89.—North Carolina, 1928. Distribution of the wheat acreage. The value of the 1928 crop of wheat is represented by one dot to each $5,000.

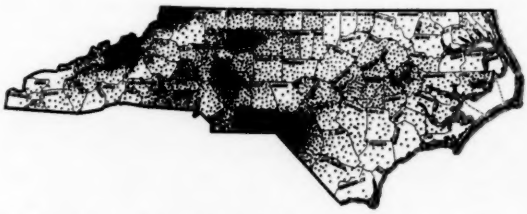


Chart 90.—North Carolina, 1928. Distribution of the oat acreage. The value of the 1928 crop of oats (grain) is represented by one dot to each $1,000.

of the incidence of 1928 to fall to levels comparable with those of 1926, though in 1928 an increase in cotton acreage would also have to be considered.

Arkansas was part of the flood area of 1927 (American National Red Cross,[3] United States Department of Agriculture [105] and United States Public Health Reports [109]), and the increased incidence of pel-

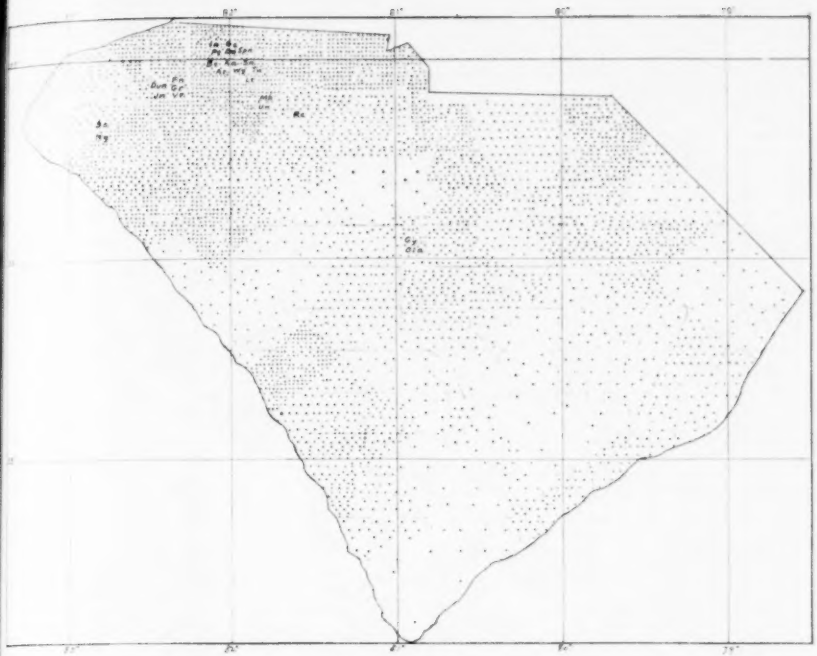


Chart 91.—Incidence and distribution of pellagra in South Carolina in 1927. (From the South Carolina State Board of Health.) The lettering indicates the approximate location of the villages studied, as reported by the Hygienic Laboratory.

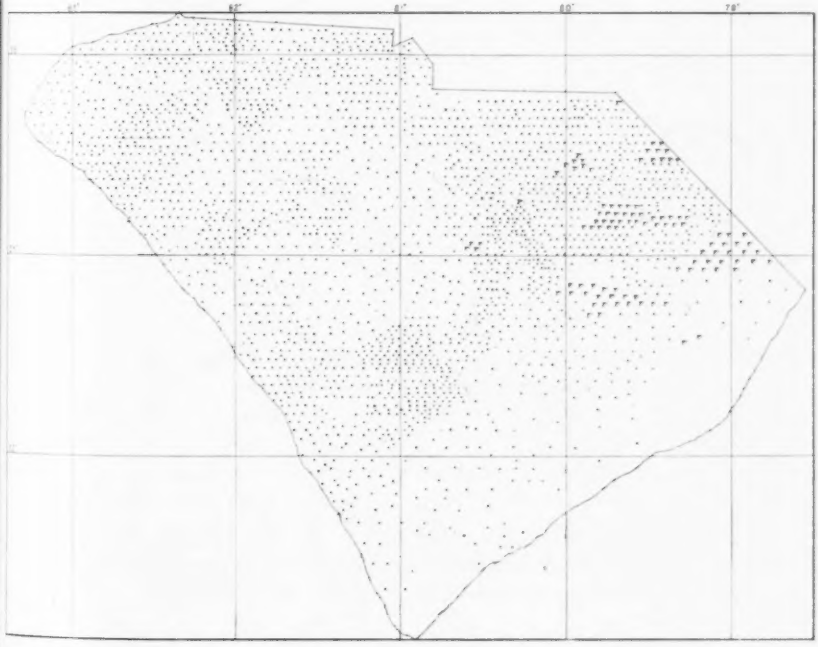


Chart 92.—South Carolina, 1927. The dots indicate the distribution of the cotton acreage (divided by 1,000); *T*, the distribution of the tobacco acreage (divided by 1,000).

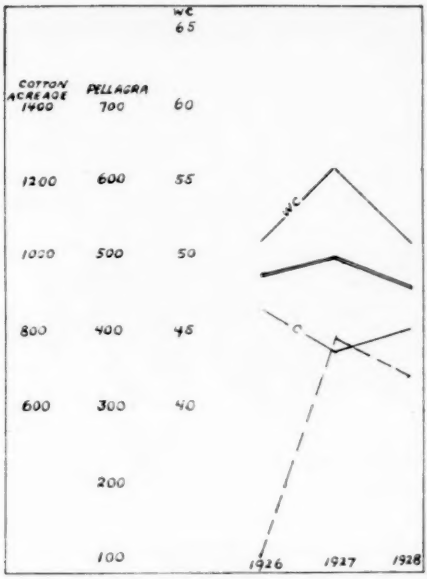


Chart 93.—Arkansas, area of Fort Smith. Curve *WC* indicates the winter cloudiness; curve *C*, the cotton acreage; the double line, the mean winter cloudiness and cotton acreage, and the broken line, the incidence of pellagra.

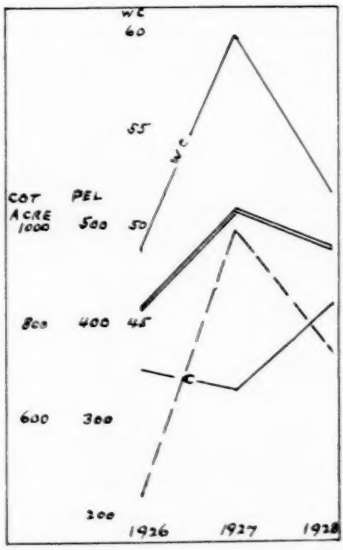


Chart 94.—Arkansas, area of Little Rock. Curve *WC* indicates the winter cloudiness; curve *C*, the cotton acreage; the double line, the mean winter cloudiness and cotton acreage, and the broken line, the incidence of pellagra.

lagra was anticipated by the United States Public Health Service on the basis of a deficiency of food and economic distress. While observation does not disparage the effectiveness of the relief work or disprove the theories on which the relief work among pella-

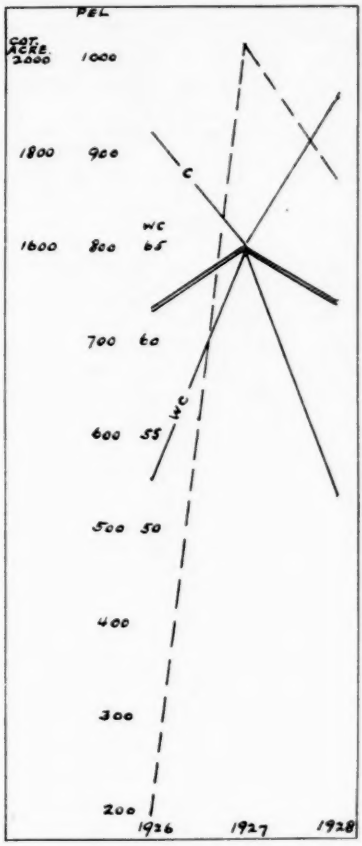


Chart 95.—Arkansas, area of Memphis. Curve *WC* indicates the winter cloudiness; curve *C*, the cotton acreage; the double line, the mean winter cloudiness and cotton acreage, and the broken line, the incidence of pellagra.

grins was based, it is of interest to note that Thatcher,[99] in a study of the conditions in Pulaski County, Arkansas, reported that Dr. Paul L. Day estimated the vitamin B content of the diet in acute cases that developed after the flood, and while the results seemed to show a

deficiency of this and other vitamins both before and after the flood, the deficiency in vitamin B was rather more marked before than after.

The available data for Mississippi are shown in charts 96, 97, 98, 99, 100 and 101. This state was also involved in the flood of 1927. It is to be noted that the scale adopted for the representation of the incidence of pellagra is ten times that of Arkansas. Figures for the cotton acreage by counties are not available for 1926, 1927 and 1928, except for ten counties in the flood area for 1926 and 1927, and these are only approximate.[105] With the use of the United States Census

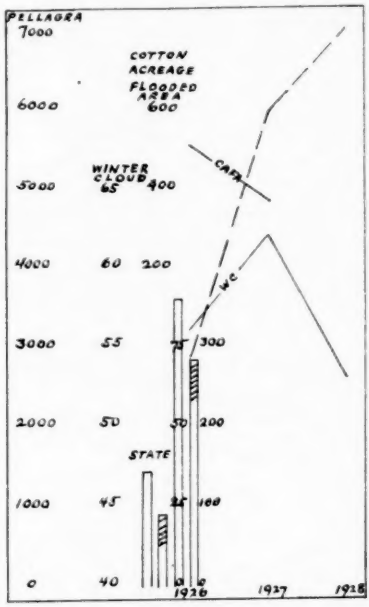


Chart 96.—Mississippi, ten flood counties. *CAFA* indicates the cotton acreage in flooded area; curve *WC*, the winter cloudiness; the broken line, the incidence of pellagra; the vertical column, plain, the average cotton acreage per county (divided by 1,000), in 1919, from the United States census, the vertical column, hatched, the average amount of pellagra per county, 1926.

figures for 1920 (for the year 1919), a striking correlation is noted between the cotton acreage in 1919 and the incidence in 1926 of pellagra (vertical shaded columns in the charts).

In regard to the possible influence of winter cloudiness and its apparent influence as compared with "momentum," a somewhat unique opportunity is afforded in this state during these years to note reversed conditions with reference to winter cloudiness in different parts of the

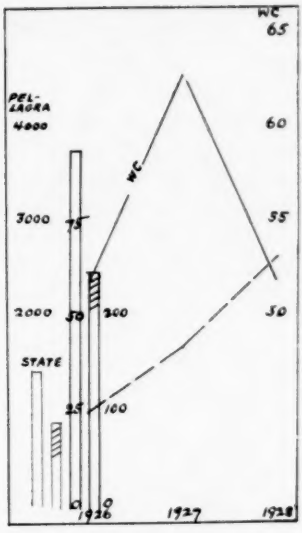


Chart 97.—Mississippi, four lesser flood counties, northern. Curve *WC* indicates the winter cloudiness; the broken line, the incidence of pellagra; the vertical column, plain, the average cotton acreage per county, 1919; the vertical column, hatched, the average amount of pellagra per county in 1926.

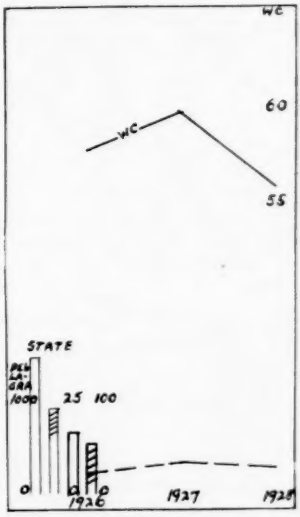


Chart 98.—Mississippi, four lesser flood counties, southern. Curve *WC* indicates the winter cloudiness; the broken line, the incidence of pellagra; the vertical column, plain, the average cotton acreage per county in 1919; the vertical column, hatched, the average amount of pellagra per county in 1926.

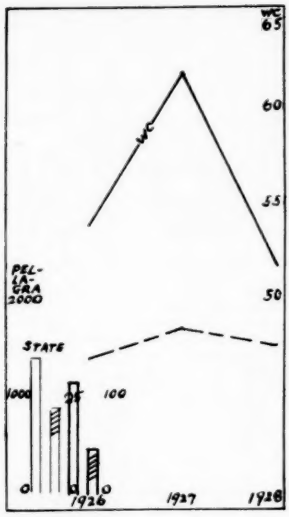


Chart 99.—Mississippi, twenty-nine northern counties. Curve *WC* indicates the winter cloudiness; the broken line, the incidence of pellagra; the vertical column, plain, the average cotton acreage per county in 1919; the vertical column, hatched, the average amount of pellagra per county in 1926.

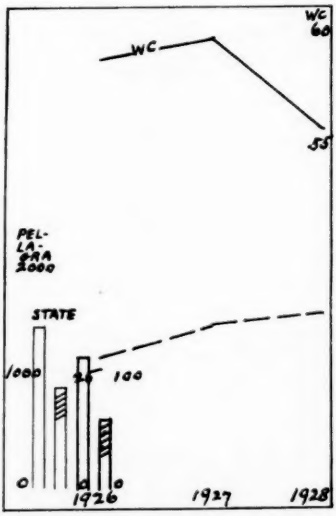


Chart 100.—Mississippi, nineteen south central counties. Curve *WC* indicates the winter cloudiness; the broken line, the incidence of pellagra; the vertical column, plain, the average cotton acreage per county in 1919; the vertical column, hatched, the average amount of pellagra per county in 1926.

state. In all sections of the state, except in sixteen southern counties, the winter cloudiness in 1927 was in excess of that in either 1926 or 1928. The area of these sixteen counties was also the only one in which the incidence of pellagra for 1927, as reported, was lower than that for 1926 or 1928 (chart 101). In general, during these three years, the incidence of pellagra conformed to the variation in winter cloudiness in all sections; however, in the fourteen northern counties included in the flood area, the incidence of pellagra for 1928 was higher than that for 1927, whereas winter cloudiness was lower. Economic conditions may have been worse in 1928 than in the year of the flood, but this

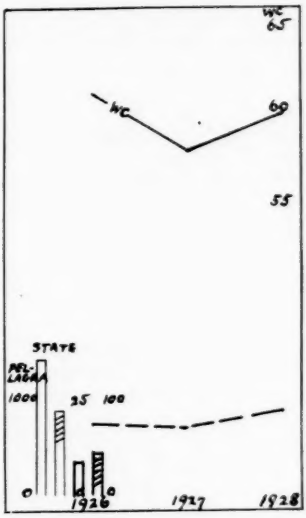


Chart 101.—Mississippi, sixteen southern counties. Curve *WC* indicates the winter cloudiness; the broken line, the incidence of pellagra; the vertical column, plain, the average cotton acreage per county in 1919; the vertical column, hatched, the average amount of pellagra per county in 1926.

would seem improbable. On the other hand, it is noticeable that these counties constitute an area of normally large cotton acreage, of high incidence of pellagra for 1926 and of a gross numerical increase in incidence for 1927 (approximately 3,100 and 700 cases, respectively, charts 96 and 97). If the increased incidence of pellagra in 1927 is considered a factor of momentum resulting in a delayed incidence, its effect is seen in the failure of the incidence for 1928 to fall; on the contrary, an actual and marked rise occurred.

Chart 102, which includes the ratios of winter cloudiness, cotton acreage in the flooded areas and the incidence of pellagra for 1926

and 1927, for the ten major counties in which the flood occurred, shows for the first seven counties a fairly consistent conformity to the positive influence of winter cloudiness and the planting of cotton on the incidence of pellagra as suggested by previous figures. Of the three other counties, two, Issaquena and Warren, reported only 8 and 59 cases of pellagra, in 1926, respectively, and therefore are hardly suitable for statistical purposes. The great increase of pellagra in Washington County in 1927 may have had some relationship to the figures given in table 21.

Whether or not the figures in table 21 embody an explanation of the relatively high ratio of pellagra in Washington County in 1927 is

TABLE 21.—*Increase of Pellagra in Counties*

County	Population in 1920 in Thousands	Population per Square Mile in 1920	Cotton Acreage in 1919 in Thousands	Crop Acreage Flooded in 1927 in Thousands	Population Affected by the Flood in Thousands	1926 Cotton Acreage Flooded in 1927 in Thousands	1927 Cotton Acreage in Flooded Area in Thousands*	Pellagra per Square Mile, 1907-1911, Inclusive	Pellagra in Whole County, 1926	Pellagra in Whole County, 1927	Pellagra in Whole County, 1928
Bolivar.....	57	65	215	96	17	75	48	0.081	774	1,167	1,842
Sunflower.....	46	68	151	92	20	76	58	0.078	582	1,060	1,169
Leflore.....	37	65	109	36	6	27	19	0.068	408	702	820
Holmes.....	34	46	73	20	6	15	9	0.071	245	467	451
Sharkey.....	14	33	42	74	14	55	37	0.040	198	406	470
Humphreys...	19	47	56	91	24	72	51	0.087	165	321	574
Yazoo.....	37	41	76	76	14	55	44	0.037	152	217	215
Washington..	51	70	134	189	55	140	108	0.142	265	1,431	1,184
Issaquena.....	7	18	23	43	8	21	14	0.001	8	52	42
Warren.....	33	58	22	21	5	14	7	0.001	59	132	168

* This column represents actually the "Acres of flood area expected to be planted in 1927" in other crops than corn and hay, as "an act of Congress specifically prohibits our publishing any report regarding intentions to plant cotton." By comparison of other sets of data on "other crops" and cotton, about 92 per cent of the foregoing figures represented cotton acreage.

not entirely clear. The population affected by the flood was much greater than that in any other county. The flooding of a high percentage of the cropland of this county may have resulted in extreme economic deprivation. Extensive planting of cotton under postflood conditions may have involved labor and exposure to midsummer solar rays in a degree not normal to the planting of cotton. The fact that in the early period, from 1907 to 1911, Washington County had a greater population per square mile and a larger incidence of pellagra per square mile than any other county in this group may be of significance. The failure of this county to show an increased incidence in 1928 also remains unexplained. Figures for the acreage of cotton for the counties of the entire state for 1926, 1927 and 1928 might throw further light on the relative incidence, but these figures have not been available.

Charts 103 and 104 show the distribution of pellagra and cotton, respectively, in Mississippi for 1926 and 1919.

Charts 105 to 126 are presented by way of a summary of the factors that have been discussed as having a possible relation to the annual incidence of pellagra in a given area. Their significance is subject to several important limitations, which will be mentioned, and doubtless to other limitations that will be apparent to expert statisticians. Variations in the scales used in different figures for the same class of data, for example, the incidence of pellagra in Virginia and in Mississippi, limit their significance to the representation of trends rather than of absolute values. Agricultural values for Virginia are

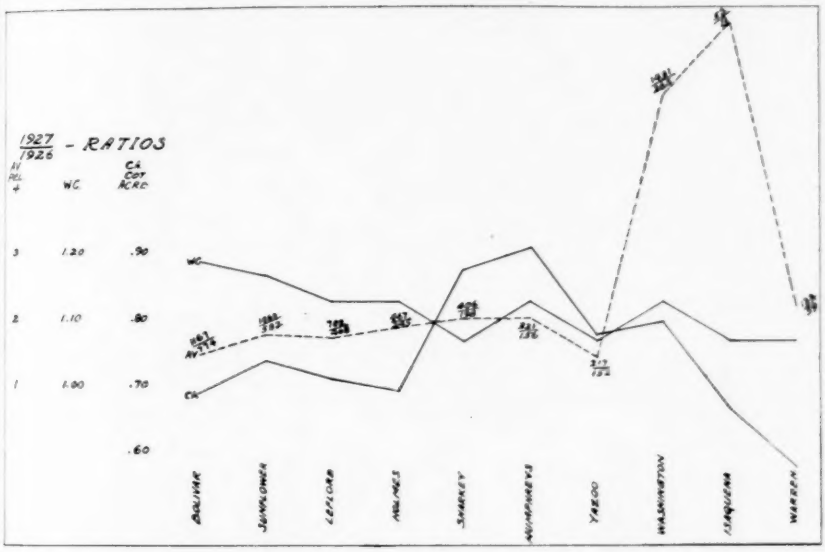


Chart 102. Ten major flood counties of Mississippi in 1927, with ratios of 1927 : 1926. Curve *WC* indicates the winter cloudiness; curve *CA*, the cotton acreage in the flooded area of each county; the broken line, the incidence of pellagra.

based on tobacco, the relatively small amount of cotton planted being ignored. For South Carolina, the crop of tobacco is ignored, and for Tennessee, the curves pertaining to the value of tobacco are shown, but are not included when means of curves are plotted. Except for Virginia, cotton is the basis of the agricultural values used.

The curve of deaths from pellagra in the United States Registration area (*Z*, chart 126) is probably more nearly in accord with actual conditions than the various curves representing the incidence of pellagra, such as *AV* in chart 126. However, certain of the reports of

the incidence of the disease would appear to have a fairly reliable accuracy in view of the fact that in the Report of the Bureau of Communicable Diseases for June, 1930, in Mississippi, the percentage of physicians reporting is given as 99.18.

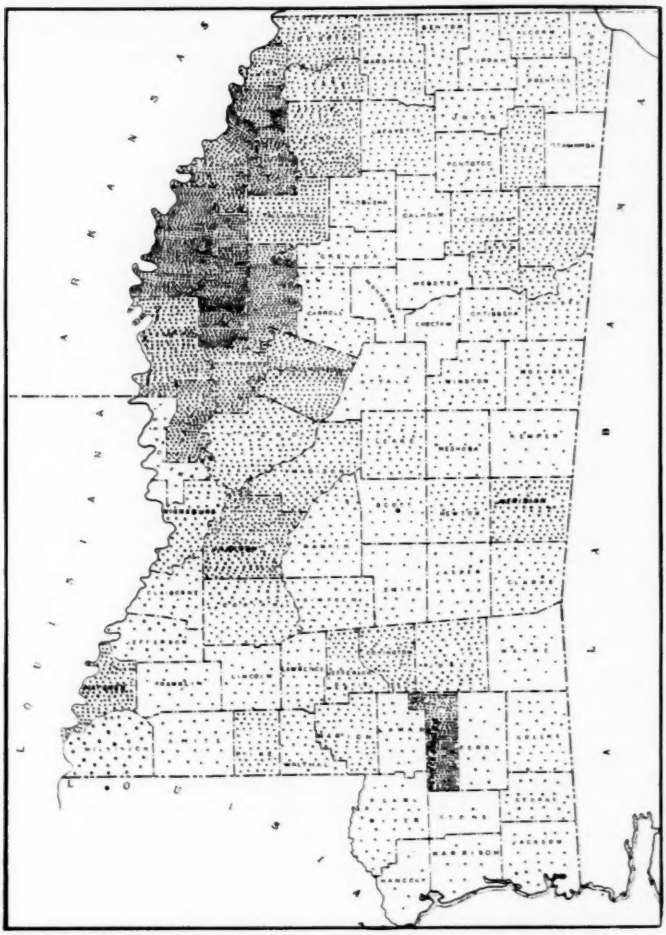


Chart 103.—Incidence and distribution of pellagra in Mississippi in 1926. (From the Mississippi State Board of Health.)

A primary assumption underlying charts 106 to 125 is that the factors determining the influence of pellagra may vary in different seasons of the year, and with respect to the eighteen charts (charts 106

to 123) for nine states, half of the figures represent the first and half the second six months of the annual cycle. Likewise, charts 124 and 125, showing composite data for four states, represent the first and second half years, respectively.

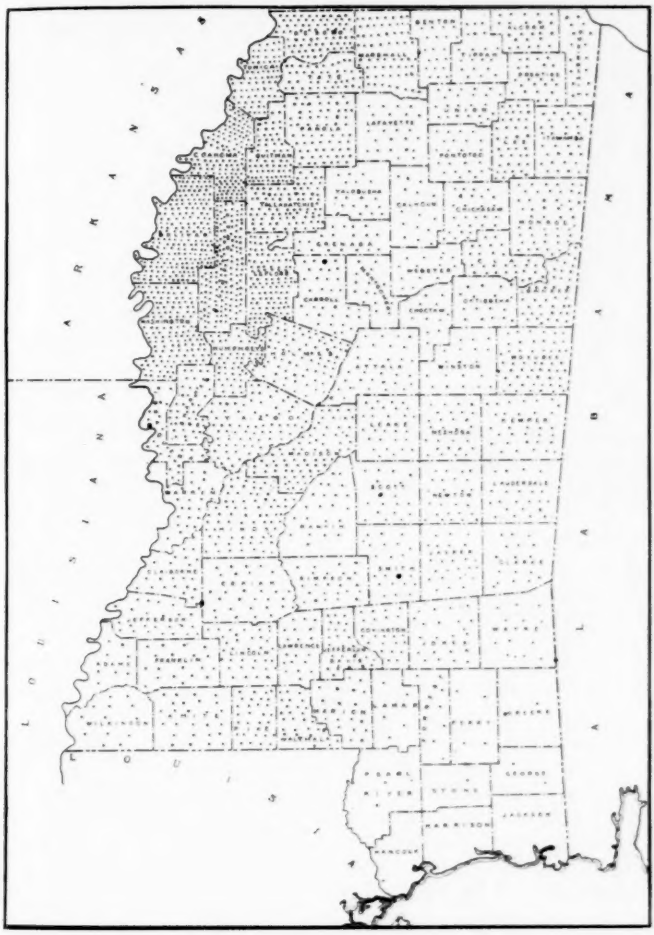


Chart 104.—Mississippi, 1919. Distribution of cotton acreage (divided by 1,000).

In view of the data already presented tending to relate the distribution of pellagra to that of the planting of cotton, an index has been sought in the economics of the cultivation of cotton that might show

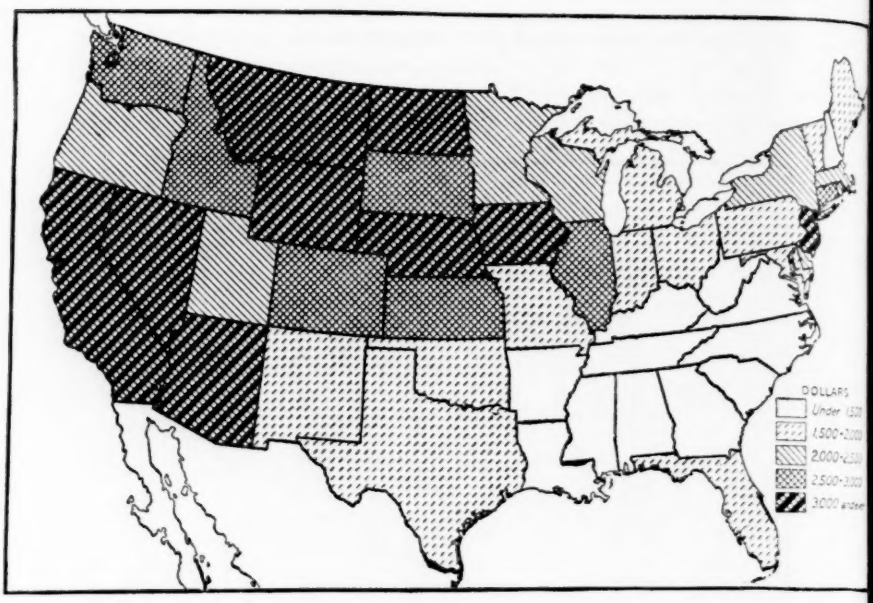


Chart 105.—Annual gross income per farm, 1924-1928. (From the United States Department of Agriculture, Yearbook of Agriculture, 1930.)

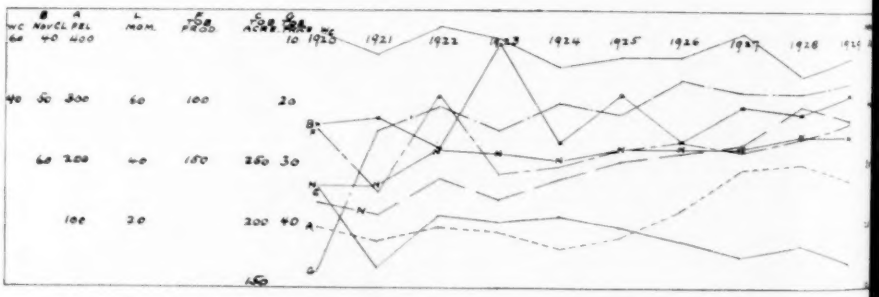


Chart 106.—Virginia, from 1920 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve *WC*, the winter cloudiness (December, January and February), an average of all stations; curve *B*, the cloudiness (sunshine) at Lynchburg the previous November; Curve *C*, the current year's tobacco acreage; curve *F*, the production of tobacco for the previous year (acreage multiplied by yield per acre); curve *G*, the previous December 1 price of tobacco; *M*, the previous November and December, current January and February incidence of pellagra; *N*, mean of November cloudiness (*B*), tobacco acreage (*C*), previous year's production of tobacco (*F*), previous December price of tobacco (*G*) and "momentum" from previous year (*M*).

some correspondence between the annual variation and annual variations in the incidence of pellagra, thus tending to illustrate and interpret the influence of economic conditions in the causation of pellagra, among the population planting cotton, as held by Goldberger and his associates—an attempt as applied to the rural population roughly parallel to the detailed study carried out by the Hygienic Laboratory (Hygienic

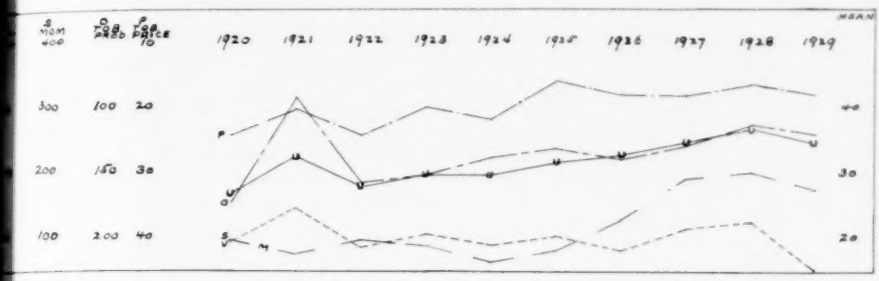


Chart 107.—Virginia, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve *O*, the production of tobacco for the current year; curve *P*, the price of tobacco for the current year; curve *S-M*, the incidence of pellagra in the first half of the current year; curve *U*, the mean of the current year's production of tobacco (*O*), the current year's price of tobacco (*P*) and the "momentum" from the first half of the current year (*S*).

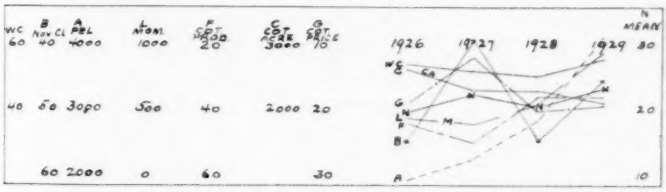


Chart 108.—South Carolina, from 1926 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve *WC*, the winter cloudiness (December, January and February), an average of all stations; curve *Bx*, the cloudiness (sunshine) at Greenville the previous November; curve *C-CA*, the current year's cotton acreage; curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre); curve *G*, the previous December 1 price of cotton; curve *L-M*, the previous November and December, current January and February incidence of pellagra; curve *N*, the mean of the November cloudiness (*B*), the cotton acreage (*C*), previous year's production of cotton (*F*), previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

Laboratory Bulletin,[45] p. 117) in cotton-mill villages in South Carolina. For this purpose the following facts seem pertinent.

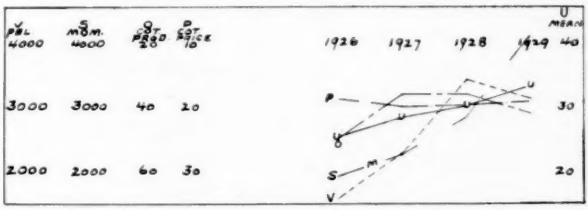


Chart 109.—South Carolina, from 1926 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve *O*, the production of cotton for the current year; curve *P*, the price of cotton for the current year; curve *S-M*, the incidence of pellagra in the first half of the current year; curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

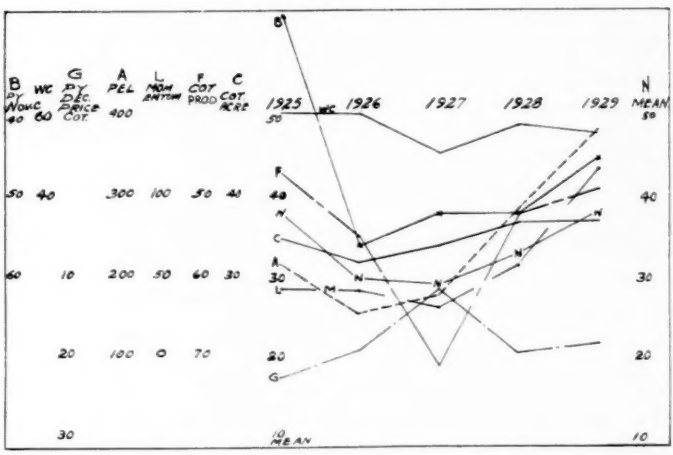


Chart 110.—Georgia, from 1925 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve *WC*, the winter cloudiness (December, January and February), an average of all stations; curve *Bx*, the cloudiness (sunshine) at Atlanta the previous November; curve *C*, the current year's cotton acreage; curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre); curve *G*, the previous December 1 price of cotton; curve *L-M*, the previous November and December, current January and February incidence of pellagra; curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

In general, the annual gross income per farm [108] is lowest in an area corresponding to the distribution of cotton and pellagra, though it is not strictly so limited (chart 105).

The cotton is planted in the late spring and early summer, and is marketed by farmers,[108] as is illustrated for 1928:

	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.	April	May	June	July
Per cent	4.6	15.6	24.8	20.8	12.8	5.4	4.0	4.8	1.8	1.6	1.9	1.9

This tabulation shows that 78.6 per cent of the crop is marketed from August to December, inclusive.

Of the farms in the cotton belt, from 50 to 66 per cent are operated by tenants.[103] These farmers and many who own their farms raise and market the crop largely through the medium of credit, with little money in hand or reserve of cash at any time of the year. These conditions suggest that during the first half of the year the economic status of the farmer who markets a single crop (cotton) depends largely on the production and price of cotton for the previous six months, and that his economic status for the second half of the year depends largely on the production and price of cotton for the current period.* For this reason, the production of cotton (acreage multiplied by yield per acre) for the previous year (*F* in the charts) and the price on the previous December 1 (*G* in the charts) have been selected as economic indexes for the first half of a current year. The curves for these factors, production and price, have been plotted separately, rather than multiplied in order to obtain a total value of the crop. Aside from *a priori* reasons that might favor plotting the curves for production and price separately, there is apparently a closer correlation between these curves so plotted and the curve of the incidence of pellagra than between a curve of the value of the entire crop of cotton and the incidence of pellagra. The scale of all economic factors is reversed so as to represent a decreased value by a rise in the curve to correspond with the suspected influence of economic depression tending to a rise in the incidence of pellagra.

* There seems to be no reasonable doubt that there is a direct correlation between the planting of cotton and the incidence of pellagra, but interpretation of the statistics introduces several possibilities. Reference has been made to exposure to sunlight as a possible positive (climatic) influence and to acreage as a factor in the value of the crop as a possible negative (economic) influence. Neither of these points of view takes into account still another consideration, viz., the extent to which the planting of cotton crowds out the planting of gardens, ownership of livestock and poultry and other agricultural pursuits tending to supply the population with pellagra-preventive foodstuffs. This phase of the economics of the planting of cotton in relation to the etiology of pellagra has been emphasized by Wheeler and others. At least it would appear that the relation of the planting of cotton to the incidence of pellagra might be advantageously subjected to further investigation.

In the second half of the year, the curve for the production of cotton (O) is the same as that in the first half (F), but is plotted currently for the year, and the curve for the price of cotton (P) represents the current price for August 1 rather than for that of the previous December (G).

In chart 126, the curves for deaths from pellagra (Z) and the incidence of pellagra (AV) represent these data for the whole year rather than for the first or second half, and the curve V represents the farm value of the cotton for the previous December 1 (acreage multiplied by yield per acre times price).

In representing climatic factors possibly related to the incidence of pellagra, the curve of winter cloudiness (WC) is plotted in connection with the data for the first half of the year for each state. Graphically,

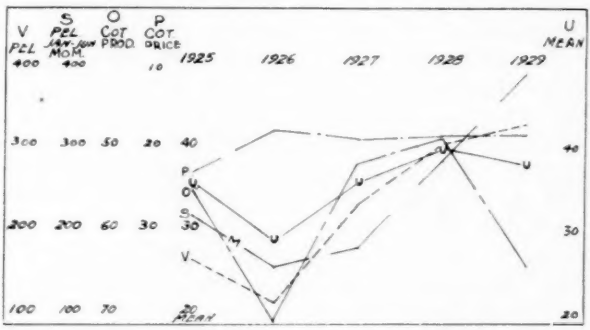


Chart 111.—Georgia, from 1925 to 1929, inclusive. Curve V indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve O, the production of cotton for the current year; curve P, the price of cotton for the current year; curve S-M, the incidence of pellagra in the first half of the current year; curve U, the mean of the current year's production of cotton (O), the current year's price of cotton (P) and the "momentum" from the first half of the current year (S).

with the exception of Virginia, a general and direct correlation is not suggested, and the curve has not been included in the means derived from the other plotted curves. There is here an apparent and possibly a real contradiction to the suggested influence of cloudiness in winter in contrast to solar exposure in summer as involving a significant principle of change from accustomed conditions. As previously stated and as illustrated by chart 24, the supposed principle of the influence of unaccustomed exposure to solar rays may have a greater validity than is indicated by the measure adopted, i. e., average cloudiness at all stations within a given state for

December, January and February, the exposure to solar rays during the spring and summer being regarded as constant. As an illustration of the possibility of a nearer approach to conditions of reality by observing a different index of shifting exposure to solar rays (charts 106, 108, 110, 112, 114, 116, 118, 120 and 122), cloudiness in the previous November at the Weather Bureau station nearest the center of the cotton belt for the state is plotted on a reversed scale, so that an upward peak indicates an excess of sunshine in November. If, in relation to this factor, winter cloudiness is regarded as constantly high,

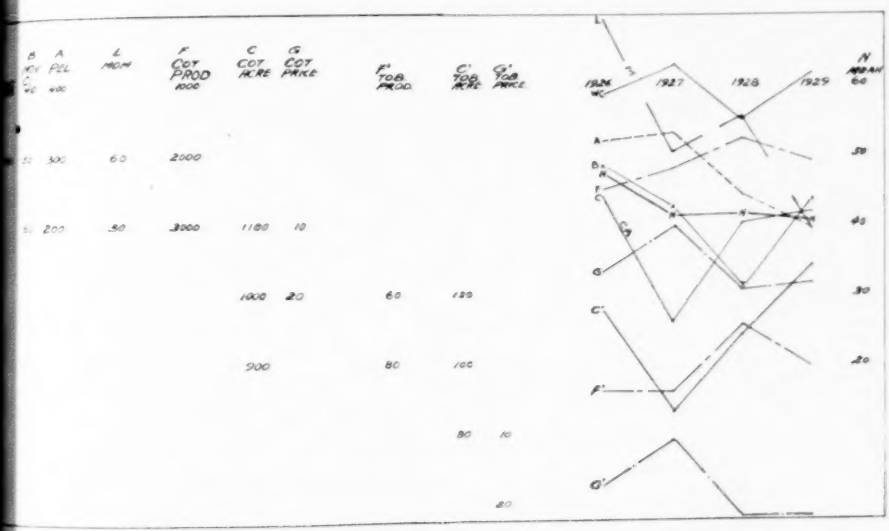


Chart 112.—Tennessee, from 1926 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve *WC*, the winter cloudiness (December, January and February), an average of all stations; curve *Bx*, the cloudiness (sunshine) at Memphis the previous November; curve *C-CA*, the current year's cotton acreage; curve *C'*, the current year's tobacco acreage, and *F*, the production of cotton for the previous year (acreage multiplied by yield per acre); curve *F'*, the production of tobacco for the previous year; curve *G*, the previous December 1 price of cotton; curve *G'*, the previous December 1 price of tobacco; curve *L-M*, the previous November and December, current January and February incidence of pellagra; curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

i. e., sunshine constantly low, there would be a change in exposure to solar rays from an excess of sunshine in November, when it occurs,

to low sunshine in winter (exaggerated in certain years, as 1927) and back again to the relatively high percentage of possible sunshine (reduced cloudiness) and relatively unfiltered solar rays (reducing air mass traversed) in spring and summer. The inclusion of this curve of previous November cloud (B) appears to favor a closer correlation of all the factors under consideration with annual variations in the incidence of pellagra than is obtained without the factor B.

Since the data presented (charts 28 to 69) indicate a close correlation between the incidence of pellagra and an increased exposure to solar rays, it would seem probable that the annual acreage of cotton planted would in some degree determine the exposure of the population planting cotton to solar rays near the summer solstice, and in this

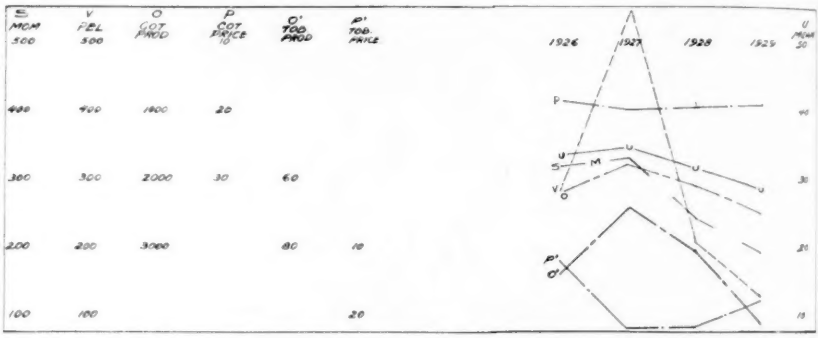


Chart 113.—Tennessee, from 1926 to 1929, inclusive. Curve V indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve O, the production of cotton for the current year; curve O', the production of tobacco for the current year; curve P, the price of cotton for the current year; curve P', price of tobacco for the current year; curve S-M, the incidence of pellagra in the first half of the current year; curve U, the mean of the current year's production of cotton (O), the current year's price of cotton (P) and the "momentum" from the first half of the current year (S).

sense would be regarded as a climatic factor as distinguished from an economic factor. The curve for this factor is plotted in charts 106, 108, 110, 112, 114, 116, 118, 120 and 122 as C, and since the supposed relation to the incidence of pellagra is direct, the scale is not reversed as it is for curves F and O, in which cotton acreage is regarded as a factor in the economics of the cultivation of cotton.

The possibility that conditions tending to the production of pellagra in one year may have an influence on the incidence of pellagra the following year has been referred to under the designation "delayed inci-

dence" or "momentum." When it is considered that the seasonal incidence of pellagra tends to reach a low level in November and to remain low till spring, it would appear that the incidence of the disease during November, December, January and February may in some degree constitute an index of this factor of "momentum," and in charts 106, 108, 110, 112, 114, 116, 118, 120 and 122 the curve *L* represents the reported incidence of pellagra for the four months named.*

In charts 107, 109, 111, 113, 115, 117, 119, 121 and 123 for the second half of the year, the incidence of pellagra during the first half of the current year has been plotted (*S*) as a similar factor of

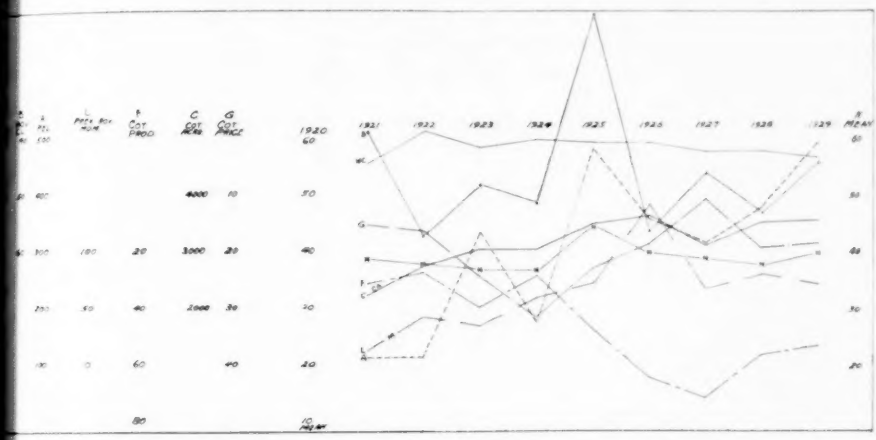


Chart 114.—Alabama, from 1921 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve *WC*, the winter cloudiness (December, January and February), an average of all stations; curve *Bx*, the cloudiness (sunshine) at Montgomery the previous November; curve *C-CA*, current year's cotton acreage; curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre); curve *G*, the previous December 1 price of cotton; curve *L-M*, the previous November and December, current January and February incidence of pellagra; curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), previous year's production of cotton (*F*), previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

"momentum," a lag or a delayed effect of influences operative during the first half of the year.

* For 1920, the incidence of pellagra for the months of January and February multiplied by 2 is used in lieu of November and December, 1919, and January and February, 1920.

Of the figures for the first half of the year, the curve N represents the mean of the two "climatic" factors B and C, the two "economic" factors F and G and the factor of "momentum" L.

Of the figures for the second half of the year, the curve U represents the mean of the two "economic" factors O and P and the factor of "momentum" S.

Charts 124 and 125 represent the first and second half years, respectively, for the four states for which data of the incidence of pellagra are available from 1920 to 1929, inclusive. Curve E (chart 124) is the mean of "climatic" factors B and C. Curve I is the mean of "economic" factors F and G. Curve N is the same curve as that described, the mean of the five factors represented by B, C, F, G and L. Curve R (chart 125) is the mean of "economic" factors O and P. Curve U is the same as that described, the mean of the three factors O, P and S.

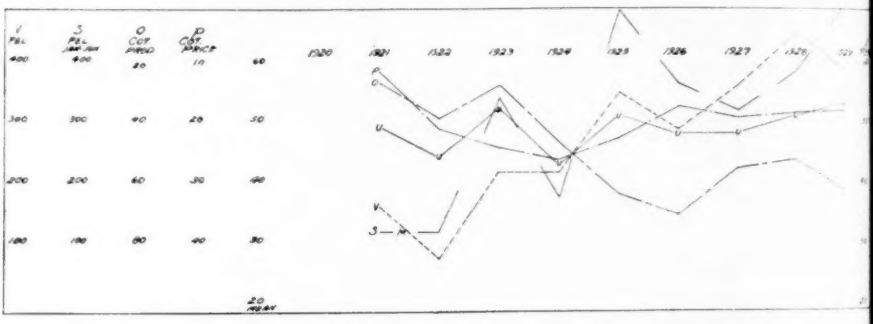


Chart 115.—Alabama, from 1921 to 1929, inclusive. Curve V indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve O, the production of cotton for the current year; curve P, the price of cotton for the current year; curve S-M, the incidence of pellagra in the first half of the current year; curve U, the mean of the current year's production of cotton (O), the current year's price of cotton (P) and the "momentum" from the first half of the current year (S).

If Mississippi (charts 116 and 117), the state with the highest reported incidence of pellagra, is selected for examination, the following observations with reference to correlations with the curve of the incidence of pellagra appear to be justified, and it is believed that they are in the main supported by the figures for other states. In chart 116, the curve of previous November cloudiness (B) is close from 1920 to 1927. The curve of cotton acreage (C) shows little annual conformity, but a conformity in a general upward trend. The curve of the production of cotton (F) is quite close in the period from 1925 to 1928. The curve of the price of cotton (G) is in rough general conformity. The

curve of "momentum" (L) is in general conformity. The curve N of the mean of the five factors mentioned appears to indicate that in the two "economic" factors, the two "climatic" factors and the factor of "momentum" the major factors bearing on the annual incidence of pellagra in a given state are comprehended. Similar observations with reference to chart 117 appear to be warranted, but a closer correlation of the curve of the price of cotton (P) from 1920 to 1925 is noted.

The exceptional peak in the incidence of pellagra (V) in the second half of the year in Arkansas in 1921 and 1927 (chart 119) is noteworthy. It would seem possible that in 1927 the delay in the planting

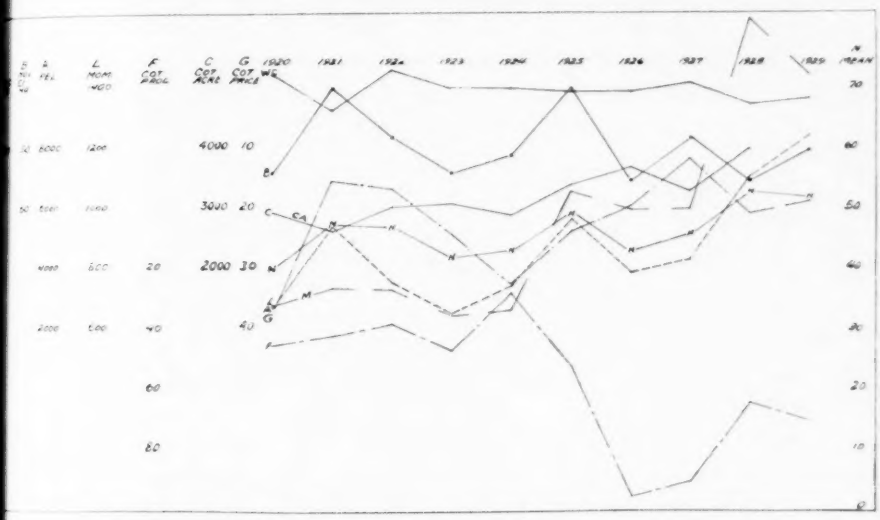


Chart 116.—Mississippi, from 1920 to 1929, inclusive. Curve A indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve WC, the winter cloudiness (December, January and February), an average of all stations. Bx, cloudiness (sunshine) at Vicksburg the previous November; curve C-CA, the current year's cotton acreage; curve F, the production of cotton for the previous year (acreage multiplied by yield per acre); curve G, the previous December 1 price of cotton; curve L-M, the previous November and December, current January and February incidence of pellagra; curve N, the mean of November cloudiness (B), cotton acreage (C), the previous year's production of cotton (F), the previous December price of cotton (G) and the "momentum" from the previous year (L).

of cotton, owing to the flood in the Mississippi Valley, might rationally require a transfer of curve C (chart 118) to chart 119 for 1927, and that this would also apply in some measure to other states included in the flood area, such as Tennessee, Mississippi and Louisiana. As for

the peak of the incidence of pellagra in the latter half of 1921 in Arkansas, in a personal communication, Dr. C. W. Garrison, State Health Officer for Arkansas, stated:

> The number of pellagra cases reported for Arkansas for August, 1921, was 1,395. The reason for this high number at that time was that I sent out a request letter and urged all cases to be reported as that was a high pellagra year following the depression of 1920. Under normal conditions a great majority of the pellagrins do not call a physician until they are bedridden.

In chart 124, the curve *N*, representing the mean of five factors (*B*, *C*, *F*, *G* and *L*), appears to correlate somewhat more closely with that of the incidence of pellagra (*A*) than does either curve *E* (of the

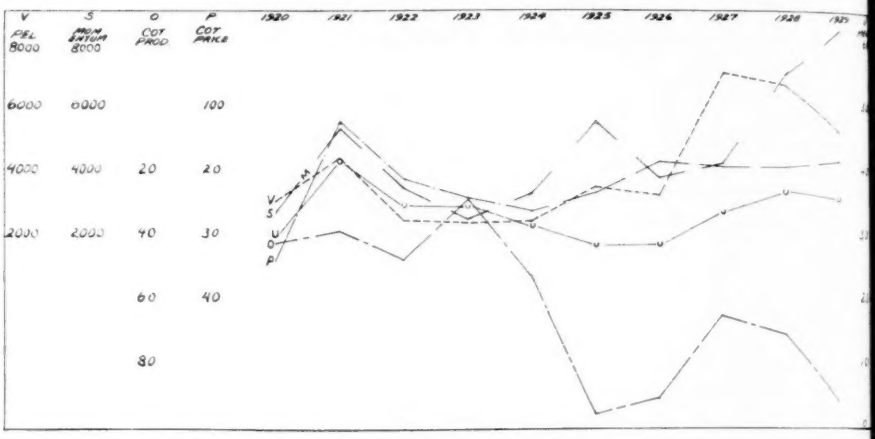


Chart 117.—Mississippi, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve *O*, the production of cotton for the current year; curve *P*, the price of cotton for the current year; curve *S-M*, the incidence of pellagra in the first half of the current year; curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

two "climatic" factors *B* and *C*) or curve *I* (of the two "economic" factors *F* and *G*). In chart 125, there is but little apparent difference in the correlation between the curve of the incidence of pellagra (*V*), curve *R* (the mean of "economic" factors *O* and *P*) and curve *U* (the mean of *O* and *P* and the factor of "momentum" *S*).

In chart 126, the interest lies chiefly in the fact that it introduces a curve of the deaths from pellagra (*Z*) in the United States Registration Area from 1913 to 1928. There is a degree of annual conformity

between this curve (Z) and the curve of the value of cotton (Y) sufficient to regard it as tending to confirm the opinion of the Goldberger school relative to the significance of economic conditions in the epidemiology of pellagra, at least with respect to annual variations. There appears to be only a rough conformity of the incidence of pellagra as reported with the mortality from pellagra as reported; it is seen more in the general trend than in the annual variation. The insert showing the relation of rural to urban deaths from pellagra from 1925 to 1927, inclusive, gives a ratio of approximately 3:1.

Humidity.—It is generally recognized that relative humidity and the temperature of the atmosphere, together with the movement of the air and intake of food, are interrelated in their effect on bodily com-

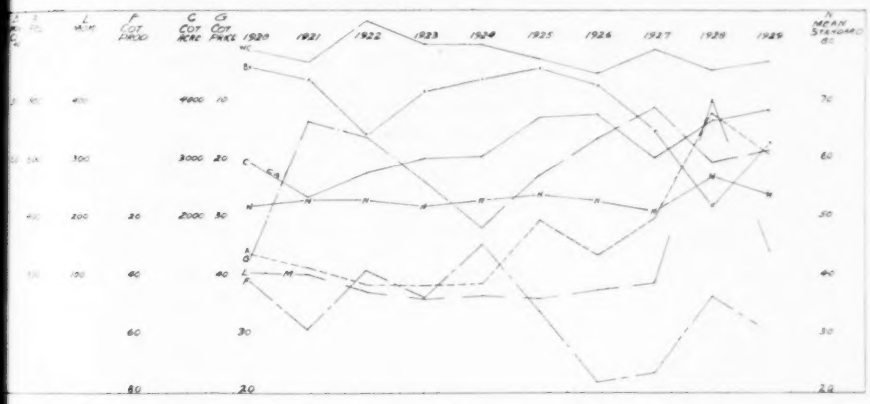


Chart 118.—Arkansas, from 1920 to 1929, inclusive. Curve A indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve WC, the winter cloudiness (December, January and February), an average of all stations; curve Bx, the cloudiness (sunshine) at Little Rock the previous November; curve C-CA, the current year's cotton acreage; curve F, the production of cotton for the previous year (acreage multiplied by yield per acre); curve G, the previous December 1 price of cotton; curve L-M, the previous November and December, current January and February incidence of pellagra; curve N, the mean of November cloudiness (B), cotton acreage (C), previous year's production of cotton (F), previous December price of cotton (G) and the "momentum" from the previous year (L).

fort, physical and mental efficiency and metabolism (Lusk[66] and McConnell, Yagloglou and Fulton[73]).

The best combination of all is probably air at about 67° F. and 80 per cent relative humidity, with a barely perceptible movement. A departure from these conditions in any direction diminishes people's comfort, reduces their capacity to work, presumably increases their susceptibility to disease, and unquestionably

raises their death rate. The most favorable condition is a variable temperature whose average is the optimum. Each month in the year the same conditions are manifest: many deaths when the temperature rises, few when it falls (Huntington [44]).

The influence of heat and humidity may extend through a twenty-four hour cycle, while that of solar radiation is limited to daylight only.

Sundstroem (quoted by Laurens [57]) found that the light from mazda lamps acts as a stimulant to the growth of mice exposed to it at ordinary

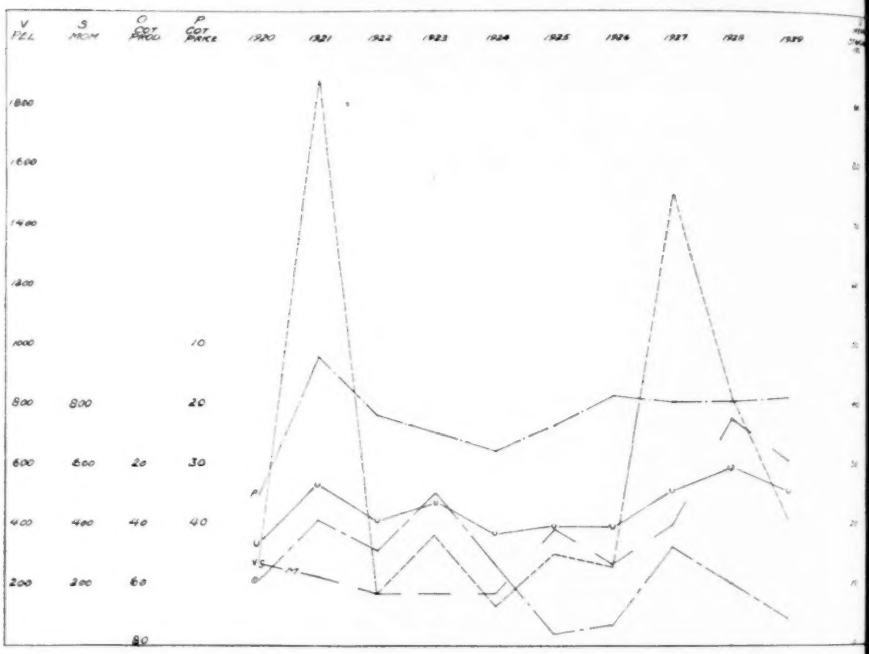


Chart 119.—Arkansas, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve, *O*, the production of cotton for the current year; curve *P*, the price of cotton for the current year; curve *S-M*, the incidence of pellagra in the first half of the current year; curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

room temperature, but the retarding influence of stagnant humid air is added to by exposure to this artificial light. He found little evidence that tropical sunlight as such had any effect on the growth of rats, the harmful effect of a tropical climate seeming to be in the decrease in the cooling power of stagnant air.

Charts 127 and 128 show that in South Carolina in 1927 and 1928 the seasonal curve of relative humidity closely approximated that of cloudiness. The same charts and chart 129 (Virginia) show a tendency to a minimum relative humidity in the spring and a maximum humidity in August. Chart 130 shows this excess of humidity in August over

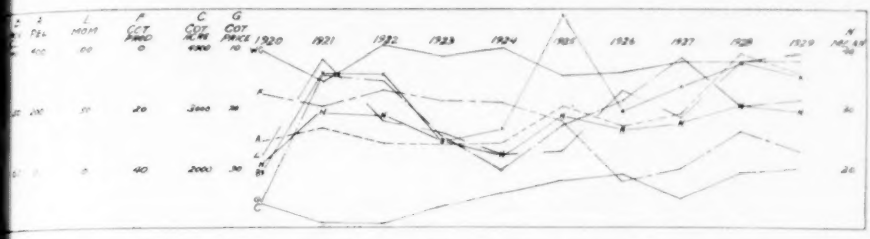


Chart 120.—Louisiana, from 1920 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve *WC*, the winter cloudiness (December, January and February), an average of all stations; curve *Bx*, the cloudiness (sunshine) at New Orleans the previous November; curve *C*, the current year's cotton acreage; curve *F*, production of cotton for the previous year (acreage multiplied by yield per acre); curve *G*, the previous December 1 price of cotton; curve *L*, the previous November and December, current January and February incidence of pellagra; curve *N*, the mean of the November cloudiness (*B*), cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

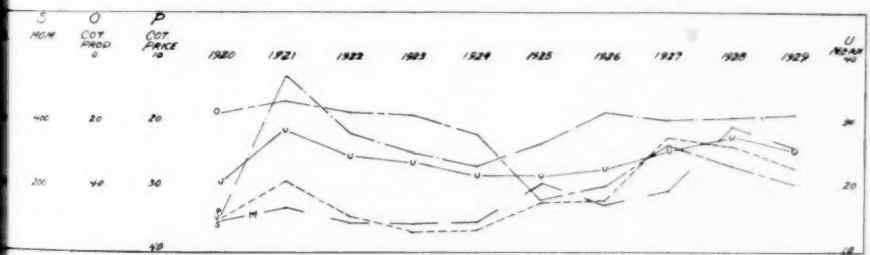


Chart 121.—Louisiana, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve *O*, the production of cotton for the current year; curve *P*, the price of cotton for the current year; curve *S-M*, the incidence of pellagra in the first half of the current year; curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

that in April as a phenomenon quite general to the pellagra belt and somewhat more accentuated in the areas with a heavier incidence of

pellagra and more planting of cotton (compare with chart 23). Chart 130 also shows the mean temperature for July in the same area. The relatively high humidity in August does not appear to depress the average metabolism during that month in Virginia (charts 21 and 22), though the rising humidity from spring through the summer may have such a tendency. It is noted also that the incidence of pellagra begins to decline before the maximum humidity is reached.

There is no apparent relation of the data shown in chart 130 to the geographic distribution and prevalence of pellagra further than that, in general, in the pellagra belt the temperature and humidity approximate the levels described by various authors as favorable to a minimum metabolism and to a low intake of protein.

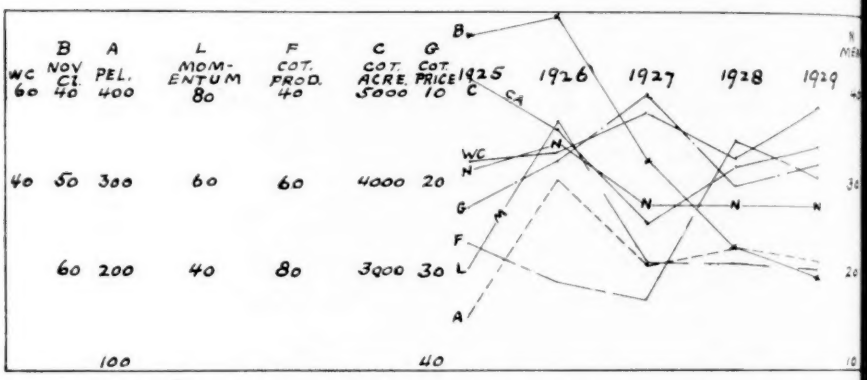


Chart 122.—Oklahoma, from 1925 to 1929, inclusive. Curve *A* indicates the incidence of pellagra in the first half year, from January to June, inclusive; curve *WC*, the winter cloudiness (December, January and February) at Oklahoma City; curve *Bx*, the cloudiness (sunshine) at Oklahoma City the previous November; curve *C-CA*, the current year's cotton acreage; curve *F*, the production of cotton for the previous year (acreage multiplied by yield per acre); curve *G*, the previous December 1 price of cotton; *L-M*, the previous November and December, current January and February incidence of pellagra; curve *N*, the mean of November cloudiness (*B*), cotton acreage (*C*), the previous year's production of cotton (*F*), the previous December price of cotton (*G*) and the "momentum" from the previous year (*L*).

AREAS WITH A RELATIVELY HIGH PREVALENCE OF PELLAGRA

Consideration has been given the seasonal and annual incidence of pellagra. It is now proposed to examine factors possibly contributing to a relatively high prevalence from year to year and from season to season in a given area. The two states with the highest reported incidence are Mississippi and South Carolina, in the order named.

Under the title of "Bulletin W," the Weather Bureau of the United States Department of Agriculture issued a summary of the climatological data of the United States by sections, from the establishment of the stations to 1920, inclusive. Section 79, for northern Mississippi, comprises that portion of the state northward of the thirty-third par-

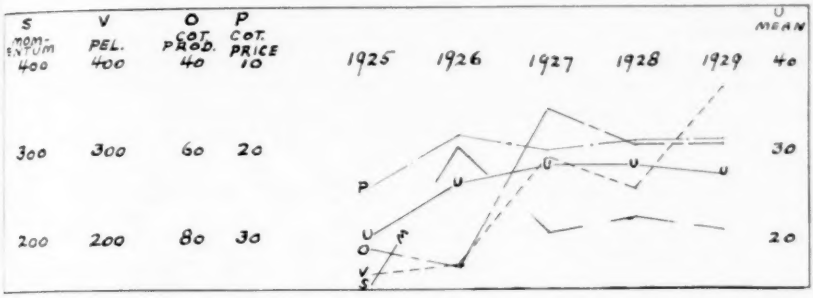


Chart 123.—Oklahoma, from 1925 to 1929, inclusive. Curve *V* indicates the incidence of pellagra in the second half year, from July to December, inclusive; curve *O*, the production of cotton for the current year; curve *P*, the price of cotton for the current year; curve *S-M*, the incidence of pellagra in the first half of the current year; curve *U*, the mean of the current year's production of cotton (*O*), the current year's price of cotton (*P*) and the "momentum" from the first half of the current year (*S*).

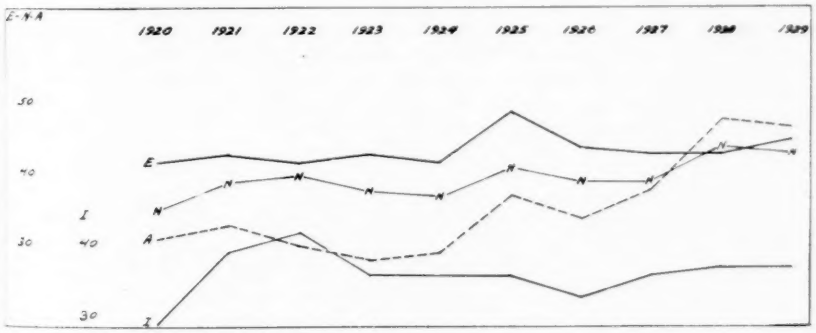


Chart 124.—Composite data for four states, Virginia, Mississippi, Louisiana and Arkansas, for the first half of the year, from January to June, inclusive, and from 1920 to 1929, inclusive. Curve *A* indicates the incidence of pellagra; curve *E*, the mean of the previous November cloudiness (sunshine) and the current year's cotton acreage; curve *I*, the mean of the production of cotton (Virginia, tobacco) for the previous year and the previous December price of cotton (Virginia, tobacco); curve *N*, the mean of November cloudiness, cotton acreage, the previous year's production of cotton, the previous December price of cotton and the "momentum" from the previous year.

allel, and section 80, for southern Mississippi, that portion of the state southward of that latitude. The general description of the northern section is as follows:

21,500 square miles, with no large urban population, the main industries being agriculture, lumbering or allied enterprises. The western portion of this division, the so-called Delta region, is mainly included between the Tallahatchie and Yazoo Rivers, on the east, and the Mississippi River on the west, an extremely fertile, level body of land, with alluvial soil, about 5,800 square miles in area. . . . The mean annual temperature of the district is 62.6°; January average temperature is the lowest, 43.9°, and July the warmest, 80.4°. The heat is somewhat alleviated at intervals during the season from the middle of May to the end of September by the occurrence of thunder showers, with subsequent drop in tem-

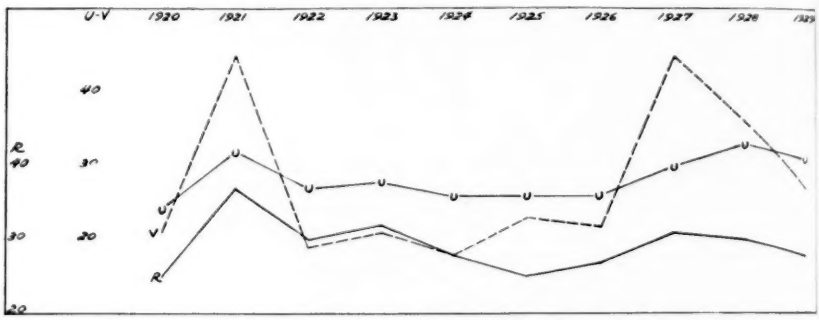


Chart 125.—Composite data for four states, Virginia, Mississippi, Louisiana and Arkansas, for the second half of the year, from July to December, inclusive, from 1920 to 1929, inclusive. Curve *V* indicates the incidence of pellagra; curve *R*, the mean of production of cotton for the current year (Virginia, tobacco), and the price of cotton for the current year (Virginia, tobacco); curve *U*, the mean of the current year's production of cotton, the current year's price of cotton and the "momentum" from the first half of the year.

perature of short duration, otherwise this heated period is very oppressive, the air continuing moist. Maximum temperatures of 100°, or higher, occur with greatest frequency during July and August, but occasionally are recorded during other months of this season.

The general description of the southern section is as follows:

There are no large cities and the main occupation is agriculture, or some allied industry. The summers are long and hot, the winters short and mild. . . . Temperatures of 100°, or over, occasionally occur in the interior in midsummer and as night temperatures are high at that time of the year, and the humidity also, with little air movement, the summer climate is somewhat oppressive. Air circulation, due to land and sea breezes, serves to alleviate the hot and humid atmospheric condition throughout the region adjacent to the coast.

It will be manifest that such a climate, whatever relations of cause and effect are or are not involved, is not unfavorable to the production of cotton and to the development of pellagra.

Examination of charts 25, 85, 91 and 103 shows the coastal areas of Virginia, North Carolina, South Carolina and Mississippi to be relatively free from pellagra. With variations in altitude, the climatic factors vary considerably as regards light, humidity (chart 130), temperature and the movement of air. The agricultural pursuits are different (charts 82, 86, 87, 92 and 104). The population hardly appears

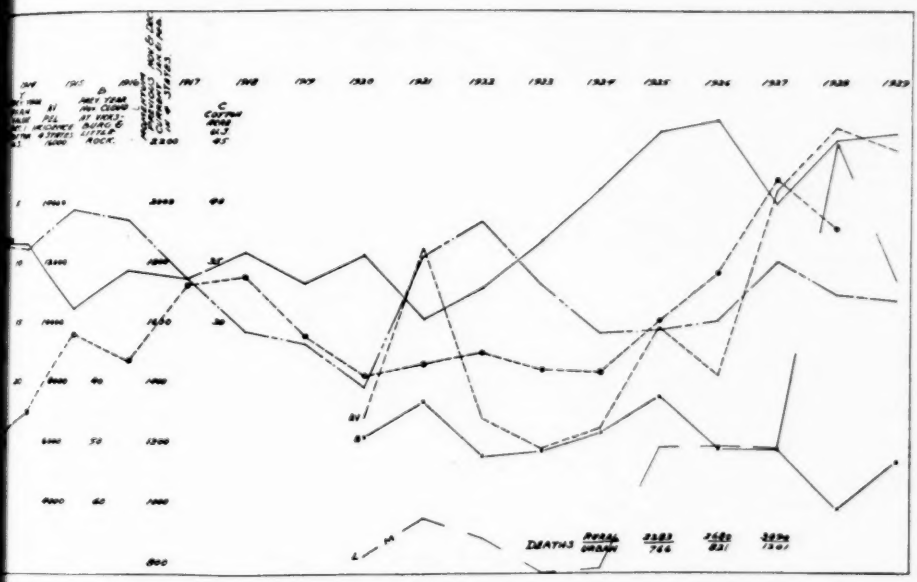


Chart 126.—Deaths from pellagra, incidence of pellagra, certain economic values and certain climatic values. Curve *Z*, indicates the deaths from pellagra in the United States Registration Area, from 1913 to 1928, inclusive; curve *AV*, the incidence of pellagra in four states, Virginia, Mississippi, Louisiana and Arkansas, from 1920 to 1929, inclusive; curve *B.r*, average of the previous November cloudiness (sunshine) at Vicksburg and Little Rock; curve *C-CA*, the current year's cotton acreage in the United States; curve *Y*, the previous December 1 farm value of cotton for the United States; curve *L-M*, the previous November and December, current January and February incidence of pellagra in four states, Virginia, Mississippi, Louisiana and Arkansas.

to be a consistent variable. The various combinations in this multiplicity of factors are numerically great and give rise to many unanswered questions. Do climatic conditions directly influence the incidence

of pellagra or may they tend primarily to influence the content of the "pellagra-preventive" factor in the vegetable and animal food of the district? Do certain climatic conditions tend to favor the production of cotton, tobacco and other crops planted in a "high sun" and thus cause excessive exposure, or do they crowd out other crops that would tend toward the prevention of pellagra? * Many of the same complex interpretations are involved in the question as to why pellagra is not more generally prevalent in the areas referred to by Huntington: "In

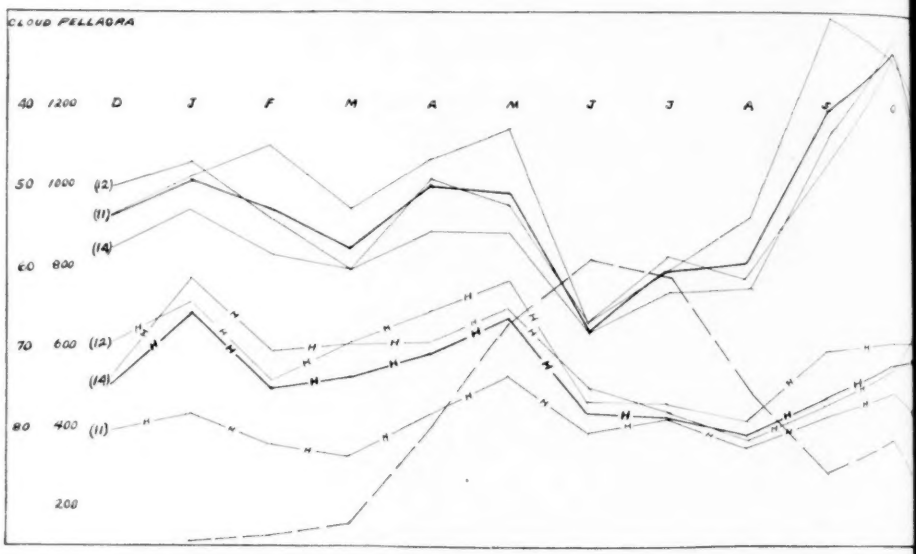


Chart 127.—South Carolina, 1927. Curve *11* indicates Charleston; *12*, Columbia; *14*, Greenville; the light continuous line, cloudiness; the heavy continuous line, the mean cloudiness; the light *H* line, the humidity; the heavy *H* line, the mean humidity; the broken line, the incidence of pellagra for the state.

the warmest regions of the world, which are also characterized in general by excess wetness, live the rice-eating peoples." [44]

From what has been said with reference to the seasonal peak of the incidence of pellagra (June), the seasonal peak of the temperature (July or August) and the seasonal peak of humidity (August), it

* In certain sections of Florida, the culture of tobacco is carried on under cover (National Geographic Magazine, reference 75), implying a tropical solar radiation and heat somewhat unfavorable to the culture of tobacco. Possibly such conditions would also favor a high incidence of pellagra, but for the relatively high percentage of solar radiation throughout the winter (charts 9 and 23).

would appear that neither temperature nor humidity has a determining influence on the peak of pellagra. On the other hand, its general coincidence with the peak of solar radiation has been shown. With reference to this factor, it is to be noted that latitude 33°, the center of the pellagra belt in the United States, bisects the state of Mississippi. The supposedly protecting sun of winter swings lower for areas farther north, and the rays of the sun in summer are more direct on areas farther south, but this latitude represents the minimum of the first and the maximum of the second that is possible of combination (chart 10).

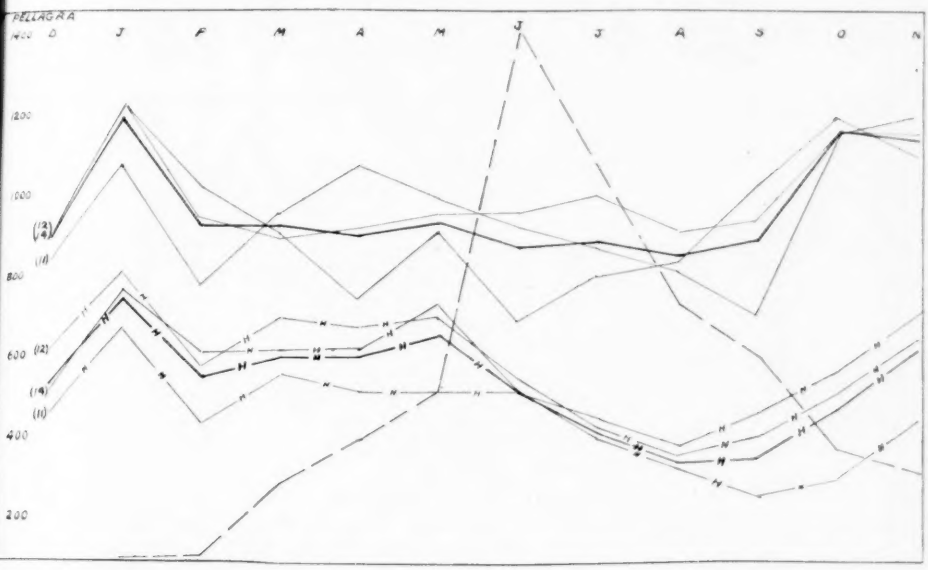


Chart 128.—South Carolina, 1928. Curve *11* indicates Charleston; *12*, Columbia; *14*, Greenville; the light continuous line, the cloudiness; the heavy continuous line, the mean cloudiness; the light *H* line, the humidity; the dark *H* line, the mean humidity; the broken line, the incidence of pellagra for the state.

Since the first census figures (1859), the centers of the production of cotton in the United States have remained within the borders of Mississippi (chart 131). This might not mean that the maximum production of cotton per square mile lies within the state, as centers to the east and to the west could give the same result, but actually as well as relatively it is the center, as is shown in table 22.[74]

If in the etiology of pellagra it is tentatively assumed that there is a genetic factor, it is to be noted that the foreign-born white population

is lowest in North Carolina (0.3 per cent) and is practically as low in Mississippi and South Carolina (0.4 per cent).[108] The Negro population may be considered to be practically all native born in the sense of southern born.

The liability of the Negro to pellagra is attested by various reports.[31] Table 23 gives a report from the Board of Health for Mississippi.

The percentage of Negro population is highest in Mississippi (52.2 per cent) and next in South Carolina (51.4 per cent) (United States Census, Mississippi [103] and South Carolina [104]).

As far as these figures go, the incidence of pellagra is higher but the mortality is conspicuously lower in the colored race than in the white race. According to Sullivan's classification, therefore, in the

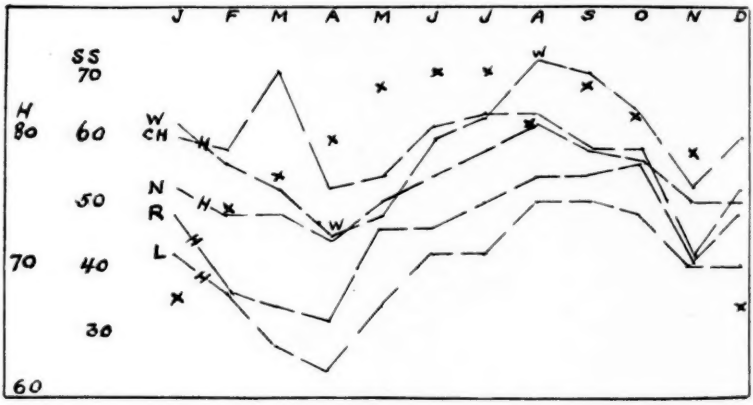


Chart 129.—Virginia. *X* indicates the average sunshine at all stations; *H*, the average relative humidity; *CH*, Cape Henry; *N*, Norfolk; *R*, Richmond; *L*, Lynchburg; *W*, Wytheville.

Negro the disease would appear to tend toward the "dermal" rather than the "systemic" type.

As a probably valid index of economic disadvantage, it may be noted that the percentage of illiterate population 10 years of age and over was 21.9 for Louisiana, 18.1 for South Carolina and 17.2 for Mississippi, which compares with geographic divisions as follows: South Atlantic, 11.5; East South Central, 12.7 and West South Central, 10.[103]

The studies of Vance [110] and of others show that the prevalence of tenant farming in the cotton belt is an index of low economic status. In Mississippi, tenant farmers number 66.1 per cent of farms, in Georgia 66.6 per cent and in South Carolina 64.5 per cent; as compared with geographic divisions: South Atlantic, 46.8 per cent; East South Central, 49.7 per cent, and West South Central, 52.9 per cent.[103]

As still another index applying more directly to food standards:

The computed average for 1928 (of home-grown food used by the farm family) was highest for Arizona ($399) and lowest for California ($145). The average was $389 for West Virginia, $306 for Iowa, $278 for Maine, $244 for Arkansas, $223 for Utah, and $205 for Mississippi (1930).[108]

Chart 132 shows the density of population by counties in Mississippi, total and rural, which corresponds rather closely with the distribution

TABLE 22.—*Production of Cotton in States Around Mississippi*

	Cotton, 1926, Running Bales	Square Miles per State, in Thousands	Bales per Square Mile, in Thousands
Alabama	1,470	51	29
Arkansas	1,513	53	28
Georgia	1,498	59	25
Louisiana	826	48	17
Mississippi	1,857	46	40
Missouri	215	..	..
Oklahoma	1,760	70	25
South Carolina	1,025	30	34*
Tennessee	442	42	11
Texas	5,477	265	21
Virginia	51	..	..
North Carolina	246	52	24

* With reference to these and other figures for Mississippi, it is of interest to note the corresponding figures for South Carolina, the second state in reported incidence in recent years.

TABLE 23.—*Liability of Negro to Pellagra*

	Pellagra, Incidence 1926	1927	1928	
White	2,363	3,491	3,667	9,521
Black	5,030	8,356	10,207	23,593
	7,393	11,847	15,874	33,114
	Pellagra, Deaths	1927	1928	
White		131	558	689
Black		99	648	747
		230	1,206	1,436

of pellagra. Chart 133 shows the percentage of Negroes in the total population, by counties, for this state.[103]

Chart 134 shows the density of population, total and rural, by counties, in South Carolina [104] (compare with chart 91, which shows the distribution of pellagra). Chart 135 shows the percentage of Negroes in the total population, by counties, for South Carolina.[104]

In Mississippi,* it would appear that at least three factors probably contribute to the relatively high prevalence of pellagra, namely, its lati-

* There is reason to believe that the thoroughness of reporting in Mississippi is superior to that in other states and that this fact must be taken into account in any comparison of incidence, prevalence or distribution of pellagra.

tudinal situation, the exposure incident to the planting of the high cotton acreage per square mile and the economic status of a portion of its population as indicated by illiteracy, tenant farming and direct statistical investigation.

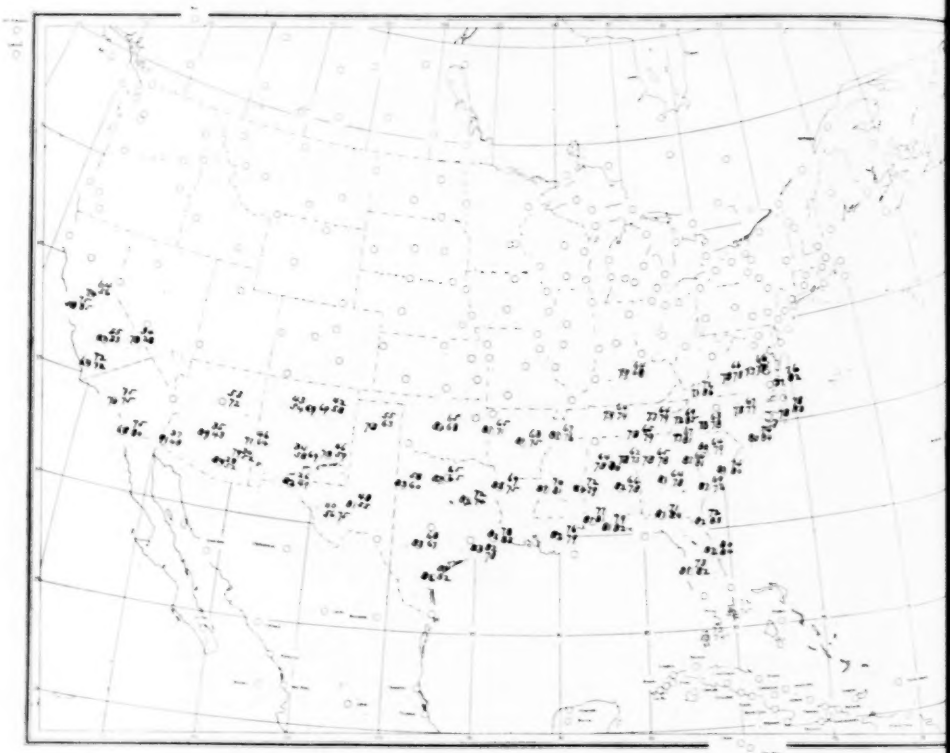


Chart 130.—The light circles indicate the location of Weather Bureau Stations. The numerals, grouped in threes, represent: the numeral on the left, mean temperature for July; the numerals on the right, mean relative humidity, above, for April, below, for August.

THE INCIDENCE OF PELLAGRA IN WORKERS IN COTTON-MILLS

Generally speaking, pellagra is a disease of rural areas both in this country and in Europe. If there is an apparent inconsistency in attributing an etiologic influence to solar rays in two groups so differently situated as planters of cotton and tobacco on the one hand and workers in cotton-mills on the other hand, the explanation is considered to lie

in the feature of relative seasonal exposure, according to which the worker in the cotton-mill would seem to be exposed to the solar rays of summer of as great intensity and duration as the planter of cotton or tobacco in proportion to the respective amounts of solar radiation received by each group in winter.

In general, it may be said that the pellagra zone begins where the zone of the siesta custom ends.

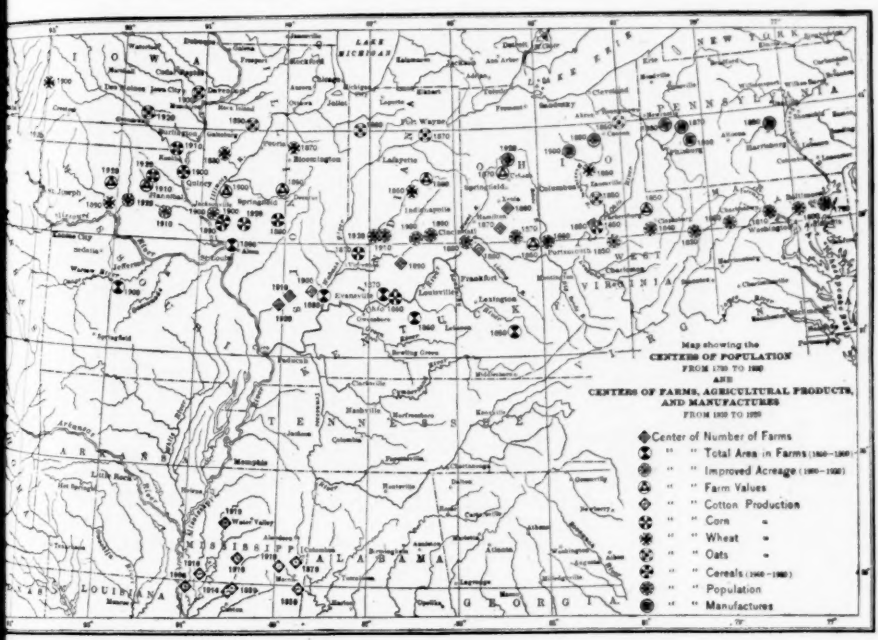


Chart 131.—Map showing the centers of population and of production, including that of cotton, from 1859 to 1919. (From the Fourteenth Census of the United States.)

If exposure to the inevitable lightly filtered solar rays of the summer season, even for irregular and brief intervals of the day and week, is deemed sufficient for the production of pellagra in the poorer classes subject to a deficiency of food, provided the deficit of sunshine in winter is relatively marked, these conditions appear to be met in workers in cotton-mills, who, as compared with the rural laborer, receive relatively little of the available sunshine in winter.

The habits of the population in cotton-mill villages are described in the following note of the Hygienic Laboratory: [45]

> It was the custom in each community studied for nearly all able-bodied persons over 14, except farmers and housewives, to work for wages. In some villages many housewives worked in the mill, but, except in the cases of young married women without children, this was usually accomplished by hiring a Negro servant to care for the house and do the cooking (p. 47).

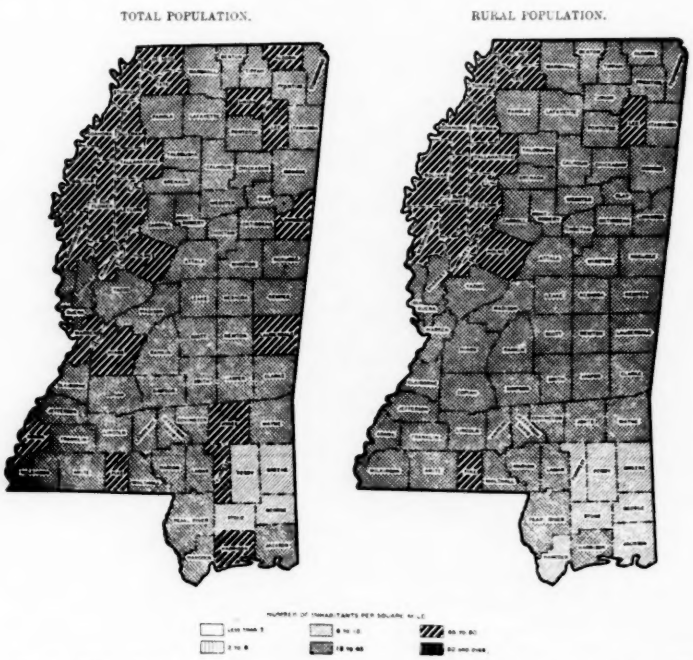


Chart 132.—Density of the population of Mississippi, by counties, in 1920. (From the Fourteenth Census of the United States.)

Rhyne [81] described the daily, weekly and annual routine of the cotton-mill worker and his economic and social status. Vance [110] gave these data as they apply to the "cropper" and tenant farmer and thus described the hereditary background, and of many the personal past, of the present-day worker in the cotton-mill.

SUMMARY

It is believed that climatic factors are important in the causation of pellagra, and that the nutritional state of the individual conditions the reaction to the solar rays.

Sulphur in the form of cystine appears to exert a protective action against exposure to solar radiation in low forms of life. Its high concentration in epidermal tissues of higher forms of animal life suggests a possible protective action in these animals also.

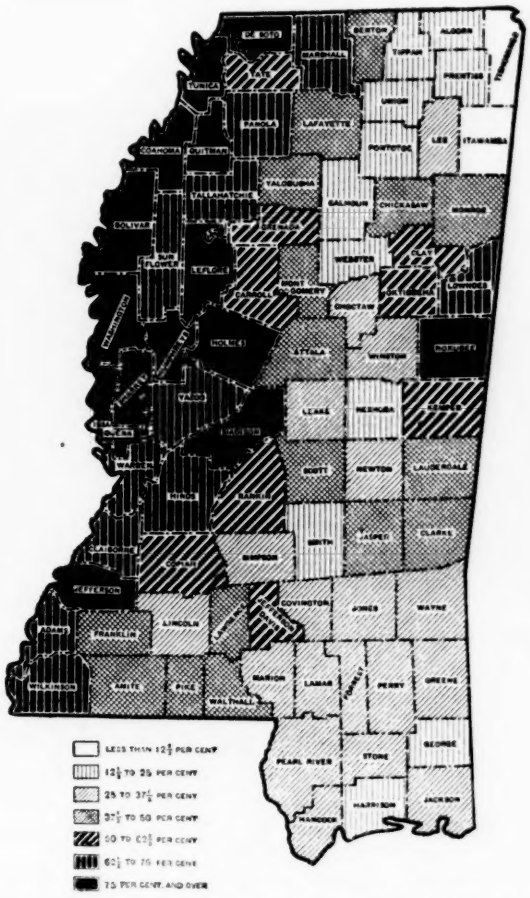

LESS THAN 12½ PER CENT
12½ TO 25 PER CENT
25 TO 37½ PER CENT
37½ TO 50 PER CENT
50 TO 62½ PER CENT
62½ TO 75 PER CENT
75 PER CENT AND OVER

Chart 133.—Percentage of Negroes in the total population, by counties, in Mississippi, in 1920. (From the Fourteenth Census of the United States.)

There is evidence to suggest that an abnormal physiologic state of the lens of the eye with reference to the normal reversible cystine ⇄ cysteine reaction, together with exposure to ultraviolet wavelengths of light, is important in the pathology of cataract. As an

illustration of the ideas developed, in this sense cataract may be thought of as pellagra of the lens.

An initial disturbance of metabolism appears to result from a variation in the amount of radiant energy acting on the organism, whether the transition is from darkness to light or vice versa.

Chart 134.—Density of the population of South Carolina, by counties, in 1920. Above, total population; below, rural population. (From the Fourteenth Census of the United States.)

In normal subjects, after ultraviolet irradiation, nitrogen equilibrium tends to be reestablished on a higher level than before, with retention of nitrogen. The disturbed metabolism of rats on a vitamin-free diet is "unable to stand the additional strain put upon it by radiation" (Eckstein).

Goldberger and Tanner thought that a deficiency of amino-acids was probably the primary etiologic factor in pellagra. The deficiency described by them was designated as a deficiency of the pellagra-preventive factor. It now appears that water-soluble vitamin B consists of at least two distinct factors, antineuritic and pellagra-preventive. These in combination, or possibly a third factor, represent the factor "bios," which is essential for the growth of animals.

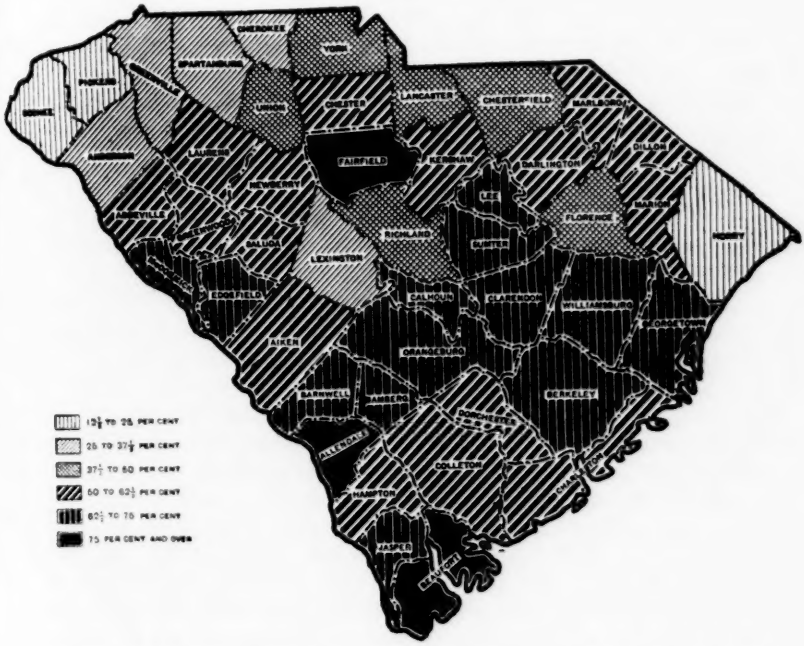


Chart 135.—Percentage of Negroes in the total population, by counties, in South Carolina, in 1920. (From the Fourteenth Census of the United States.)

A possible relation of a deficiency in supply or utilization of the sulphur-containing amino-acid cystine to the etiology of pellagra is more probable if it is assumed that solar radiation is also a factor in the etiology of pellagra. Cystine is protective against ultraviolet radiation. It promotes the growth of the yeast containing vitamin B. Its rôle is related to oxidative processes and to the detoxification of cyanogen compounds, both of which functions are disturbed in pellagra. It is necessary to the growth and maintenance of animals and is important in the nuclear activity of cell division. It is the chief source of supply for the sulphur demands of the organism. After starvation the feeding

of an adequate diet results in the retention of sulphur. Glutathione (cystine in combination with glutamic acid) was originally isolated by Hopkins from yeast and from muscle and liver. The occurrence of cystine has been remarked in the foods that Goldberger and his associates advocate as preventive of pellagra, and they contain cystine (or sulphur) in proportions comparable to the value assigned by Goldberger in the prevention of pellagra. The evidence is suggestive that a lack of cystine may have a specific relation to the etiology of pellagra.

The protective value of pigment against the superficial effects of solar rays is a matter of common knowledge. Pigmentation is essentially the deposit of melanin, high in sulphur content. Pigmentation protects against sunburn, but not against pellagra. The cutaneous lesions of pellagra, while not limited to exposed areas, occur chiefly on exposed parts, and when exceptions occur the site of the exceptional lesion is usually on parts that phylogenetically may be considered exposed and related in function to a dissipation of heat by evaporation (the scrotum of man and the scrotum and tongue of dogs—black tongue).

The dermatitis of pellagra might conceivably be a local manifestation in the production of which exposure to solar rays was an important factor, and yet solar radiation might not have a relation to the deeper and more essential changes in the diseased tissues. That such is probably not the case is suggested by the fact that pigmentation does not protect against pellagra as it does against sunburn, by the greater mortality in the race (white) that is more susceptible to the erythemal effect of the sun's rays and should therefore more readily show mild forms of the disease, by the skepticism of experienced clinicians concerning pellagra sine pellagra and by the rarity of sore tongue, diarrhea and symptoms referable to central nerve changes in the absence of dermatitis. Laurens expressed the belief that "the only reasonable conclusion is that, following ultraviolet irradiation, some photochemical substance formed in the skin is carried by the blood stream to . . . various organs, there bringing about the observed changes." In connection with commercial photography, Sheppard found that the photosensitivity substance of gels from animal hides lay in the doubly bonded sulphur as represented by allyl-isothiocyanate (mustard oil); in other words, in sulphur as it occurs in cystine.

The sick organism is a much more delicate mechanism than the well, diseased tissue being more susceptible to radiation than normal (Laurens). "We may assume that normal tissue acts like a slow (photographic) plate and diseased tissue like a fast one" (Clark). These are doubtless important considerations in connection with the known fact that the sites of predilection for the cutaneous lesions of pellagra are exposed surfaces.

The theory of a deficiency of food as the cause of pellagra and a relation between this deficiency and the economic status seem to be well established principles in the etiology of pellagra. A specific deficiency may be involved, such as of amino-acids, and possibly cystine, but this does not rule out the rôle played by the level of basal metabolism, which in turn may be influenced by a lowered intake of protein and a corresponding reduction in the "specific dynamic action" of the ingested food. Further, the intensity of the solar radiation may play a part in the etiology of pellagra through a lowered intake of protein, a direct effect on the general level of metabolism or a specific metabolic influence, such as an altered metabolism of cholesterol, nitrogen or sulphur, and the effect of a given intensity of solar radiation may depend on other factors, such as the nutritive state of the subject and variation from the intensity of recent previous exposure to solar rays.

When viewed with special reference to sulphur metabolism, the chemical analysis of pellagra may begin with the suggestion of Sullivan and his co-workers, in 1919 and 1920, that sulphur metabolism in pellagra is abnormal. The restoration of a normal exogenous sulphur (and nitrogen) metabolism in the patient who has recently had pellagra is not immediately accompanied by restoration of a normal endogenous sulphur (and nitrogen) metabolism. The excretion of thiocyanate in the urine and saliva is decreased, as is the excretion of creatinine in the urine, but Voegtlin found neutral (unoxidized) sulphur increased in the urine. In the central nervous system a loss of neutral sulphur in the cerebrum and spinal cord is described by Koch and Voegtlin, together with an increase of this constituent in the cerebellum. The various observations quoted indicate at least an abnormality of sulphur metabolism in pellagra. While the general depression of oxidative processes in pellagra may not be related to sulphur metabolism (glutathione), Bodansky and Levy found that an adequate supply of cystine was necessary to maintain an unimpaired cyanide-detoxifying power in the pellagrin.

Hypochlorhydria is usual in pellagra, and achlorhydria with an absence of pepsin is common. Pepsin apparently is necessary for the digestive alteration of the protein molecule so as to produce a nitroprusside reaction. Abderhalden suggested that pepsin and trypsin affect the molecule of albumin at different parts and that pepsin probably splits the S-S compound by forming groups of SH, SH.

In Goldberger and Wheeler's experimental pellagra in white male convicts, the relative influence of diet and solar light was apparently not taken into account. The lesions of the skin appeared primarily and chiefly on the scrotum, and Goldberger and Wheeler suggested that the site of at least the initial dermatitis is bound up with a specific quality

of diet. If both dietary deficiency and exposure to solar rays are usual factors in the etiology of spontaneously developing pellagra, Goldberger and Wheeler's data suggest that the results obtained by them represented an instance of exaggerated dietary influence as compared with the influence of solar light, and it would be suggested as a possibility that this inbalance in causation determined the site of the major lesions of the skin on the heavily pigmented, unexposed genitals, highly endowed as to function for the loss of heat through evaporation.

Goldberger and Wheeler hold that black tongue in the dog is the analog of pellagra in the human subject. Observations similar to those just made with reference to their experimentally produced pellagra seem appropriate in connection with their experimental black tongue, emphasized somewhat by the fact that the scrotal lesions experimentally produced in dogs have never been recorded in the spontaneously developing disease. The heat-dissipating function of the dog's tongue, the usual site of conspicuous lesions in black tongue, is well known and seems to represent an analog in the functional sense to the skin of the human subject.

A series of three comparisons is made as follows: (1) spontaneous pellagra and Goldberger's convicts, (2) spontaneous black tongue and Goldberger's dogs and (3) Enright's Germans and Bigland's Ottomans, prisoners of war in Egypt. In each of the three comparisons it would seem that when dietary deficiency is obvious and outstanding (the second instance in each group) in comparison with exposure to light, the effect partakes of a general or systemic reaction or type (defined by Sullivan as "systemic" as opposed to a "dermal" type in which the cutaneous lesions are relatively conspicuous), dermal effects readily attributable to direct exposure to light are at a minimum, scrotal lesions are relatively high, and mortality, when it can be compared, is great.

Koch and Voegtlin carried out experiments on rats and monkeys, observing the chemical and histologic changes in the central nervous system as a result of a restricted vegetable diet. They noted that, in general, the changes observed, including their studies of the sulphur fractions, corresponded somewhat closely to those observed in pellagra. While the authors did not ascribe a significance to the influence of sunlight, their tables clearly show the extent of exposure of the monkeys to sunlight and appear to warrant the notation of an inverse correlation between the hours of exposure and the duration of life and a critical influence of short exposures following dietary restriction and previous exposure to sunlight.

Analysis of the age and sex incidence of pellagra reveals a striking direct correlation with the age period and sex of child-bearing. On

the other hand, at either extreme of life the incidence tends to be somewhat higher in the male, possibly being associated with his more exposed outdoor life.

A curious parallel is noted between the age and sex incidence of pellagra and the tendency to excrete creatine in the urine. Characteristic of children of both sexes, the male ceases to show the tendency early, while the female, during pregnancy and in an intermittent fashion probably related to the menstrual cycle, continues to excrete creatine. In the adult male, creatinuria is rather a phenomenon of starvation or disease, especially of muscular dystrophies. In general, creatinuria appears to be indicative of a departure from the relative fixed and stable metabolism of the normal adult male. Hunter stated that "the avidity . . . of the muscle for creatine and its efficiency as a machine develop together, and as they develop, creatine disappears from the urine." Harding and Young suggested that creatine is a derivative of cystine. In this sense, creatinuria would be regarded as a departure from the normal metabolism of cystine in the adult male. At least it is known that during pregnancy there are large positive gains in the storage of sulphur. Koch and Voegtlin reported that from infancy to maturity a shift takes place in the sulphur fractions in the central nervous system, with a decrease in neutral sulphur in favor of protein sulphur. The age and sex incidence of pellagra affords interesting parallels with certain features of metabolism, but the significance of those referred to is far from clear.

The geographic distribution of pellagra is limited rather closely to the isothermal line of 80 F. average July (in the northern hemisphere) temperature, and the areas along this line where pellagra is endemic, generally speaking, are also in an isothermal belt of from 40 to 50 F. average January (in the northern hemisphere) temperature. However, any influence that this characteristic climatic feature has may not be essentially thermal, but may be mediated through such secondary features as the ultraviolet wavelength content of the solar rays or the determining influence of the climate on agriculture.

Certain features of the physics of light have been reviewed with special reference to ultraviolet wavelengths. Actual measurements of seasonal variations in intensity, as reported (chart 13), conform quite closely to a curve representing the seasonal variation in the air mass traversed by the solar rays at the corresponding latitude (in the north temperate zone) (chart 10). With the air mass held constant, pyrheliometric measurements at Naples and Florence, Italy, show that at Naples (a nonpellagrous area) the heat intensity of the solar rays is highest in winter, thus tending to offset the increased filter thickness of the air mass in winter and, therefore, to equalize the exposure to the solar rays

throughout the annual cycle. At Florence (located toward the pellagra area), with the air mass held constant, the seasonal variations in the intensity of heat tend to conform to the variations dependent on the air mass (greatest in summer), thus tending to an exaggeration in the degree of variation in the intensity of the solar rays in summer as compared with that in winter. An erythemal effect of ultraviolet rays is well established. Tisdall and Brown have furnished experimental evidence of maximal diurnal and seasonal variations in the antirachitic effect of ultraviolet solar rays.

The data at hand suggest that there are seasonal variations in the average basal metabolism of the population of a given area, but that these seasonal variations are not the same for different latitudinal belts in the same hemisphere.

In the far north, metabolism seems to be lowest in winter.

In the tropics, there is no evidence of any marked seasonal variation, and there is no marked seasonal variation in this part of the earth's relation to the sun.

In the latitude of the southern United States, metabolism seems to be lowest in summer, and the curve of average metabolism seems to be roughly in direct relation to the curve of the air filter, with certain departures, as in August, to correspond with variations in water vapor (chart 22).

In the latitude of Boston and Chicago, the data are conflicting, but taken as a whole they might be considered consistent as a latitudinal group if there is actually a reversal in the season peaks, respectively, in latitudes farther north and farther south, as the present data seem to suggest.

A constantly lower level of metabolism is probably characteristic of warm climates as compared with cold climates. Almeida suggested that in sufficient time all the factors which modify the total metabolism will finally alter the value of the basal metabolism. This idea leads to the consideration of a hereditary level of metabolism or a genetic factor affecting the habitual rate and its possible bearing on the development of pellagra.

According to Laurens' suggestion that the metabolic effects of ultraviolet irradiation are of greatest significance when taken into consideration with the accustomed exposure to these rays, the stationary population of any area is subject to deviation in at least three ways in the amount of radiation received from the sun: (1) variation in the altitude of the sun and the thickness of the air filter (annual regularity and seasonal variation), (2) variation in cloudiness (annual irregularity and seasonal irregularity) and (3) variation in exposure to the available sun in winter and to the inevitable sun in summer (annual irregularity and seasonal irregularity).

Examination of the distribution of pellagra in the United States with reference to the idea of a determining influence of the relation between maximum and minimum exposure to solar rays during the annual cycle (under certain abnormal conditions of nutrition) appears to indicate that, so far as the sun's angle is concerned, solar rays have a pellagra-producing effect in areas receiving them at an angle of 75° 30′ or above, but in view of the relatively low prevalence of the disease in the tropics, a more efficient peliagra-preventive effect would be attributed to solar rays reaching the earth's surface at no time of the year below an angle of 38° 30′.

With further reference to a protective influence of winter sunshine within the pellagra belt in the United States, in areas where there is no deficit of winter sunshine below 70 per cent of the possible sunshine (longitude, from 101° to 105° W.), pellagra is not prevalent; where there is a slight deficit below 70 per cent but not as much as 10 per cent (Florida and California), there were less than 100 cases of pellagra per state reported in any year from 1926 to 1928, inclusive, and in areas in which there was a deficit of winter sunshine of from 10 to 27 per cent below the standard of 70 per cent (from the Atlantic coast to longitude 101° W.), there were 500 or more cases of pellagra per state for each of the three years (chart 23).

Examination of the seasonal incidence of pellagra in nine southern states revealed a marked tendency for the curve of the incidence of pellagra to rise and fall with the decreasing and increasing air filter (chart 51); if the curve of ultraviolet intensity at Davos, Switzerland (chart 13), is considered as applicable to these states, the tendency is for the seasonal incidence of pellagra to rise and fall with increasing and decreasing intensity of ultraviolet radiation, or, if the curve tentatively presented as that of the average basal metabolism in Virginia (chart 22) is considered as applicable generally to the southern United States, the tendency is for the seasonal incidence of pellagra to rise and fall in the direction opposite to the rise and fall of the average basal metabolism. The larger the number of cases of pellagra in a given state for a given year, the closer these parallels tend to be. Therefore, the peak of the incidence of pellagra is usually near the summer solstice. The month of the peak may follow the summer solstice or it may precede it, but as far as the observations go, it does not precede the peak of sunshine or the absence of cloudiness so far as this peak occurs prior to the summer solstice.

A secondary rise or peak following the summer solstice is not seen save when there is a corresponding absence of cloudiness or a relative rise in the percentage of sunshine. In general, the curve for pellagra deviates from that for the air filter to correspond with that for excess

sunshine (chart 49). Doubtless in August as many persons have a tissue metabolism favorable to the development of pellagra as in either July or September, but lack whatever influence there may be in a relatively greater solar radiation.

The clinical progress of the disease is generally similar to the curve of incidence—spring onset, summer exacerbation and improvement in the fall and winter. The decline of the season of prevalence sets in only after the advent of a decline of the sun toward the south.

The distribution of pellagra in the southern part of the United States appears to be closely correlated with the distribution of the planting of cotton and tobacco, more generally cotton (charts 103 and 104). At least three possible explanations may be considered. These crops are planted at or near the summer solstice. The states in which these pursuits are followed are numbered among the states with the lowest average income per farm. The planting of any crop on a large scale tends to reduce the production of other crops and in this instance tends to crowd out the raising of foodstuffs.

With reference to variations in the annual incidence of pellagra in a given state or county, there are data to suggest that high winter cloudiness (low percentage of the possible sunshine) and high November sunshine (low percentage of cloudiness) tend to an increased incidence of pellagra during the following year. Both of these conditions involve deviation from a standard annual exposure to solar rays. There are also data to suggest that an increased cotton or tobacco acreage tends to an increase in the incidence of pellagra, though this factor (regarded here as climatic, involving exposure to the solar rays of summer) appears at times, indeed usually, to have an inherent offset in itself by reason of its contribution to the value of the crop (regarded as an economic index tending to influence nutrition).

Still another factor that appears to influence the incidence of pellagra in a given year is the incidence in the same area during the previous six or twelve months. Whatever may be the conditions favorable to a high incidence of pellagra, it would seem to be a reasonable assumption that conditions operating broadly to produce a high incidence in any given year would tend to affect an indefinite number of persons who, whether the disease did or did not develop in them during the current year, would be somewhat more liable to the disease the following year than would have been the case had the conditions of the current year been less favorable to a high incidence. Statistically, there is valid objection to considering along with supposed etiologic factors one expression of the incidence of pellagra when the effect under consideration is another expression of this incidence. This objection is regarded as somewhat less valid in view of the tendency for the incidence of pellagra to approach zero in the winter.

As indexes of the economic status of the population planting cotton (and tobacco), the production of cotton (acreage multiplied by yield per acre) and the price of cotton realized by the farmer have been used in comparison with annual variations in the incidence of pellagra. At times, the correlation appears to be quite close, and in general it is suggestive of a relationship of depressed economic conditions to the incidence of pellagra.

A division of the year into first and second halves appears to favor correlation of the several factors mentioned with the incidence of pellagra in corresponding periods of time. When all the data are considered, the correlation between the incidence of pellagra and the several factors combined (climatic, economic and "momentum") appears to be closer than the correlation between any one or any more limited combination of these factors (charts 116 and 117).

Unusual conditions, such as the flood in the Mississippi Valley area in 1927, appear to influence the correlation of the incidence of pellagra with factors considered as climatic—winter cloudiness and cotton planting —the latter, through delay in planting, tending to an increased incidence in the latter half of the year. It seems probable also that such a disaster would influence the incidence through economic stress and nutritional lack, as was anticipated and positively regarded by the United States Public Health Service.

There is not an apparent relation of temperature and humidity to the geographic distribution and prevalence of pellagra further than that in general, in the pellagra belt, temperature and humidity approximate the levels described by various authors as favorable to a minimum metabolism and to a low intake of protein.

Coastal areas appear to be relatively free from pellagra (chart 103). This may be due to certain known climatic features, to certain known differences in agricultural pursuits as compared with more inland areas or to other and unknown factors.

The highest reported incidence of pellagra in the United States is in Mississippi. In addition to superior thoroughness in reporting, at least three factors would appear to be contributory to a relatively high incidence in this state, namely, its latitudinal situation that results in the maximum of summer directness and the maximum of winter obliquity of solar rays that is possible of combination, its high cotton acreage per square mile (in excess of all other states) and the economic status of a portion of its population, as indicated by illiteracy, tenant farming and the computed average of food used by the families on the farms.

In a study of the incidence of pellagra in cotton-mill villages in South Carolina, the Hygienic Laboratory found evidence of

economic fluctuations apparently conditioning the nutritive state of the population. In addition, if exposure to the inevitable lightly filtered solar rays of the period of the summer solstice, even for irregular and brief intervals of the day and week, is deemed sufficient for the production of pellagra in the classes of population subject to a deficiency of food, provided the deficit of winter sunshine is relatively marked, these conditions appear to be met in workers in cotton-mills who, as compared with the rural laborer, receive relatively little of the available winter sunshine.

There may be significance in the fact that the pellagra zone begins where the zone of the siesta custom ends.

In general, this study is intended as a basis for further experimental work and as a basis for contemporary observation as suggested by analysis of past events. However, under controlled experimentation and observation with a limited number of subjects, there would remain the possibility that the sampling or selection of subjects failed to take into account some undetermined factor of individual metabolism present in some but not in others of the general population and conditioning the end-result. Such an explanation may account for the fact that a condition that was considered to be pellagra developed in only six of Goldberger and Wheeler's subjects used for experimentation.

CONCLUSIONS

That there are biologic effects due to radiant energy is not open to question, and that some of these are related to pellagra seems probable.

An adequate supply and a normal metabolism of sulphur appear to exert a protective influence against the pathologic effects of solar irradiation. The evidence suggests that an inadequate supply of sulphur as cystine is an important cause of pellagra, and that the abnormal metabolism of sulphur is an important feature of pellagra.

The distribution of pellagra and the variations in its prevalence and incidence suggest that solar irradiation, under certain abnormal conditions of nutrition, is an important factor in the etiology of pellagra, and that the reaction to solar rays not only is conditioned by the nutritive state, but depends on a state of the tissues determined by contrasts in degree and intensity of exposure during the annual cycle.

BIBLIOGRAPHY

1. Abderhalden, E.: Ztschr. f. phys. Chem. **83**:444, 1913.

2. Adami, J. G.: Principles of Pathology, Philadelphia, Lea & Febiger, 1910, vol. 1, p. 969.

3. American National Red Cross: The Mississippi Flood Disaster of 1927, p. 107.

4. Arkansas Annual Reports, 1926, 1927 and 1928: Arkansas Department of Mines, Manufactures and Agriculture, U. S. Department of Agriculture.

5. Benedict and Carpenter: Carnegie Inst. Washington, Pub. no. 261, 1918, p. 114.

6. Bigland, A. D.: The Pellagra Outbreak in Egypt: I. Pellagra Among Ottoman Prisoners of War, Lancet **1**:947 (May 1) 1920.

7. Blaschko, A.: Deutsche med. Wchnschr. **46**:512, 1920.

8. Bodansky, M., and Levy, M. D.: Studies on the Detoxification of Cyanids: I. Some Factors Influencing the Detoxification of Cyanids in Health and Disease, Arch. Int. Med. **31**:373 (March) 1923.

9. Britton, S. W.: Studies on Conditions of Activity in Endocrine Glands: Adrenin Secretion on Exposure to Cold, Together with Possible Explanation of Hibernation, Am. J. Physiol. **84**:119, 1928.

10. Bruman: Chem. Abst. **24**:1893, 1930.

11. Burge, W. E.: Am. J. Physiol. **36**:21, 1915; **39**:335, 1915.

12. Burge, W. E., and Wickwire, G. C.: The Decrease in Sugar Metabolism and Destruction of Insulin by Ultra-Violet Radiation, J. Biol. Chem. **72**:827, 1927.

13. Cannon, W. B., and others: Studies on Conditions of Activity in Endocrine Glands: Rôle of Adrenal Secretion in Chemical Control of Body Temperature, Am. J. Physiol. **79**:466, 1927.

14. Cason, T. Z.: The Progress of Medical Research in the South, Ann. Int. Med. **2**:309, 1928.

15. Clark, J. H.: The Physiological Action of Light, Physiol. Rev. **2**:277, 1922.

16. Cohn, E. J.: The Physical Chemistry of the Proteins, Physiol. Rev. **5**:349, 1925.

17. Cori, G. T., and Cori, C. F.: The Fate of Sugar in the Animal Body: V. A Seasonal Occurrence of Ketonuria in Fasting Rats Accompanied by Changes in Carbohydrate Metabolism, J. Biol. Chem. **72**:615, 1927.

18. Cowgill, G. R., in Billings-Forchheimer: Therapeusis of Internal Diseases, George Blumer edition, New York, D. Appleton & Company, 1928, p. 72.

19. Dakin, H. D.: Physiological Oxidations, Physiol. Rev. **1**:394, 1921.

20. Davis and Withers: U. S. Bur. of Standards, 1922, bull. 439.

21. Detlefsen, J. A.: The Inheritance of Acquired Characters, Physiol. Rev. **5**:244, 1925.

22. DuBois, E. F.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1924.

23. Dworkin, S., and Finney, W. H.: Artificial Hibernation in the Woodchuck, Am. J. Physiol. **80**:81, 1927.

24. Emerson, H., and Phillips, E. B.: Human Biology and Racial Welfare; The Influence of Urban and Rural Environment, New York, Paul B. Hoeber, Inc., 1930, p. 361.

25. Enright, J. I.: Pellagra Outbreak in Egypt: II. Pellagra Among German Prisoners of War; Observations upon the Food Factors in the Disease, Lancet **1**:998 (May 8) 1920.

26. Evvard, J. M.; Dox, A. W., and Guernsey, S. C.: Am. J. Physiol. **34**:312, 1914.

27. Fay, M., and Mendel, L. B.: Nitrogen and Sulphur Metabolism in the Dog, Am. J. Physiol. **75**:308, 1926.

28. Fuhs, H.: Wien. klin. Wchnschr. **33**:707, 1920.

29. Gardner, J. A., and Gainsborough, H.: Studies on Cholesterol Content of Normal Human Plasma: Attraction of Proteins of Plasma for Sterols, Biochem. J. **21**:147, 1927; Relationship of Plasma Cholesterol and Basal Metabolism, Brit. M. J. **2**:935, 1928.

30. Goldberger, J., and Tanner, W. F.: Amino-Acid Deficiency Probably the Primary Etiological Factor in Pellagra, Pub. Health Rep. **37**:462, 1922.

31. Goldberger, J., and Wheeler, G. A.: Experimental Pellagra in White Male Convicts, Arch. Int. Med. **25**:451 (May) 1920.

32. Goldberger, J., and Wheeler, G. A.: Experimental Black Tongue of Dogs and Its Relation to Pellagra, Pub. Health Rep. **43**:172 (Jan. 27) 1928.

33. Goldschmidt, M.: Arch. Ophth. **93**:447, 1917.

34. Gradle, H. S.: The Age of Patients Operated on for Senile Cataract, J. A. M. A. **95**:774 (Sept. 13) 1930.

35. Gross, E. G., and Steenbock, H.: Creatinuria, Arginine and Cystine as Precursors of Creatine, J. Biol. Chem. **47**:33, 1921.

36. Gustafson, F. L., and Benedict, F. G.: The Seasonal Variation in Basal Metabolism, Am. J. Physiol. **86**:43, 1928.

37. Hafkesbring, R., and Collett, M. E.: Day to Day Variations in Basal Metabolism of Women, Am. J. Physiol. **70**:73, 1924.

38. Hammett, F. S.: An Interpretation of Malignant Growth Based on the Chemistry of Cell Division, Arch. Path. **8**:575 (Oct.) 1929.

39. Harding, V. J.: Metabolism in Pregnancy, Physiol. Rev. **5**:279, 1925.

40. Harris, F. I., and Hoyt, H. S.: Science **46**:318, 1917.

41. Hess, A. F.; Lewis, J. M., and Rivkin, H.: Status of Therapeutics of Irradiated Ergosterol, J. A. M. A. **93**:661 (Aug. 31) 1929.

41a. Hopkins, F. G., and Harris, L. J.: On Glutathione: A Reinvestigation, J. Biol. Chem. **84**:269, 1929.

42. Hrdlička, A.: Human Biology and Racial Welfare: Human Races, New York, Paul B. Hoeber, Inc., 1930, p. 156.

43. Hunter, A.: Physiology of Creatine and Creatinine, Physiol. Rev. **2**:586, 1922.

44. Huntington, E.: Human Biology and Racial Welfare: The Effect of Climate and Weather, New York, Paul B. Hoeber, Inc., 1930, p. 296.

45. Hygienic Laboratory Bulletin: A Study of Endemic Pellagra in Some Cotton-Mill Villages of South Carolina, 1929, no. 153.

46. Illinois Pellagra Commission: Pellagra in Illinois, Arch. Int. Med. **10**:123 (Aug.) 1912.

46a. Kahn, Max, and Goodrich, F. G.: Sulfur Metabolism, Philadelphia, Lea & Febiger, 1926, p. 254.

47. Kendall, E. C.: Activation of Cysteine with Oxygen and Sulphur, Proc. Staff. Meet., Mayo Clin. **2**:292, 1927.

48. Kennedy, R. E.: An Economic and Social Survey of Wise County, University of Virginia Record Extension Series, May, 1928, vol. 12, no. 11.

49. Kentucky State Board of Health: Bulletin, August, 1919, p. 8.

50. Kimball, H. H.: Measurements of Solar Radiation Intensity and Determinations of Its Depletion by the Atmosphere, with Bibliography of Pyrheliometric Observations, Monthly Weather Review, U. S. Dept. Agric., Weather Bureau **55**:155 (April) 1927.

51. Kimball, H. H.: The Distribution of Energy in the Visible Spectrum of Sunlight, Skylight and the Total Daylight, International Commission on Illumination, September, 1928.

52. Koch, F. C., and Sugata, H.: Sulphur Metabolism in Yeast, Proc. Soc. Exper. Biol. & Med. **23**:764, 1926.

53. Koch, M. L., and Voegtlin, C.: I. Chemical Changes in the Central Nervous System as a Result of Restricted Vegetable Diet, Hyg. Lab. Bull., 1916, no. 103; II. Chemical Changes in the Central Nervous System in Pellagra, ibid.

54. Kruse, H. D., and McCollum, E. V.: Biochemical Investigation of Vitamin B, Physiol. Rev. **9**:126, 1929.

55. Kunde, M. M.: After Effects of Prolonged Fasting on Basal Metabolic Rate, J. M. Research **3**:445, 1923.

56. Annotations: Pellagra at Port Said, Lancet **2**:412, 1920.

57. Laurens, H.: The Physiological Effects of Radiation, Physiol. Rev. **8**:1, 1928.

58. Lavinder, C. H.: The Prevalence and Geographic Distribution of Pellagra in the United States, Pub. Health Rep. **27**:2076, 1912.

59. Lewis, H. B.: Sulfur Metabolism, Physiol. Rev. **4**:394, 1924.

60. Lewis, H. B.: Metabolism of Sulfur: Effect of Repeated Administration of Small Amounts of Cystine, J. Biol. Chem. **65**:187, 1925.

61. Lewis, H. B.: Metabolism of Sulfur: III. The Relation Between the Cystine Content of Proteins and Their Efficiency in the Maintenance of Nitrogenous Equilibrium in Dogs, J. Biol. Chem. **42**:289, 1920.

62. Lewis, H. B.; McGinty, D. A., and Root, L. E.: Metabolism of Sulfur: V. Cysteine as an Intermediary Product in the Metabolism of Cystine, J. Biol. Chem. **53**:349, 1922.

63. Lewis, H. B.; Updegraff, H., and McGinty, D. A.: Metabolism of Sulfur: VI. The Oxidation of Cystine in the Animal Organism; Second Paper, J. Biol. Chem. **59**:59, 1924.

64. Lightbody, H. D., and Lewis, H. B.: The Relation of the Protein and Cystine Content of the Diet to the Growth of Hair in the White Rat, J. Biol. Chem. **82**:485, 1929.

65. Lovett, B. R.: Quantitative Relation of Serum Albumin and Globulin, Arch. Path. & Lab. Med. **4**:984 (Dec.) 1927.

66. Lusk, G.: Science of Nutrition, ed. 3, Philadelphia, W. B. Saunders Company, 1923.

67. MacLeod, J. J. R.: Physiology and Biochemistry in Modern Medicine, ed. 4, St. Louis, C. V. Mosby Company, 1922, p. 658.

68. Macy, I. G.; Hunscher, H. A.; Nims, B., and McCosh, S. S.: Metabolism of Women During the Reproductive Cycle, J. Biol. Chem. **86**:17, 1930.

69. Mills, C. A.: Diabetes Mellitus: Is Climate a Responsible Factor in the Etiology? Arch. Int. Med. **46**:569 (Oct.) 1930.

70. Mitchell, H. H.: The Nutritive Value of Proteins, Physiol. Rev. **4**:469, 1924.

71. Morgulis, S.: Sulphur Metabolism and Partition of Sulphur in the Urine of Fasting Dogs, J. Biol. Chem. **77**:627, 1928.

72. McCollum, E. V.: Human Biology and Racial Welfare; The Reaction to Food, New York, Paul B. Hoeber, Inc., 1930, p. 343.

73. McConnell, W. J.; Yagloglou, C. P., and Fulton, W. B.: Basal Metabolism Before and After Exposure to High Temperatures and Various Humidities, Pub. Health Rep. **39**:3075, 1924.

74. North Carolina Farm Forecaster, 1928-1929, p. 26.

75. National Geographic Magazine **57**:54 (Jan.) 1930.

76. Okada, S.: Sakurai, E.; Ibuki, T., and Kabeshima, H.: Basal Metabolism in Vitamin B Starvation, Arch. Int. Med. **40**:292 (Sept.) 1927.

77. Ornstein, I.: Cholesteremia in Pellagra, Compt. rend. Soc. de biol. **93**: 793, 1925; abstr., J. A. M. A. **85**:1675 (Nov. 21) 1925.

78. Phillips, U. B.: Life and Labor in the Old South, Boston, Little, Brown & Company, 1929.

79. Reimann, S. P.: Use and Reasons for the Use of Thiocresol to Stimulate Wound Healing, J. A. M. A. **94**:1369 (May 3) 1930.

80. Remington, C.: Relation Between Cystine Yield and Total Sulphur in Various Animal Hairs, Biochem. J. **23**:726, 1929.

81. Rhyne, J. J.: Some Cotton-Mill Workers and Their Villages, Chapel Hill, University of North Carolina Press, 1930.

82. Rowe, A. H.: Refractometric Studies of Serum Proteins in Nephritis, Cardiac Decompensation, Diabetes, Anemia, and Other Chronic Diseases, Arch. Int. Med. **19**:354 (March) 1917.

83. Schamberg, J. F.: Known and Unknown About Psoriasis, J. A. M. A. **83**:1211 (Oct. 18) 1924.

84. Schamberg, J. F.: Prog. Med. **3**:222 (Sept.) 1929.

85. Schmidt, C. L. A., and Clark, G. W.: The Fate of Certain Sulfur Compounds When Fed to the Dog, J. Biol. Chem. **53**:193, 1922.

86. Scott, L. C.; Turner, R. H., and Mayerson, H. S.: Spectrographic Examination of Pellagrins' Sera, Proc. Soc. Exper. Biol. & Med. **27**:27, 1929.

87. Shelley, H. M.: Pellagra in Nyasaland, Lancet **1**:74, 1927.

88. Sheppard, S. E.: Photographic Sensitivity: A Colloid Chemical Problem, Colloid Symposium Monograph, III, New York, Chemical Catalog Company, Inc., 1925, p. 76.

89. Siler, J. F.; Garrison, P. E., and MacNeal, W. J.: Thompson-McFadden Pellagra Commission, Arch. Int. Med. **14**:289 (Sept.) 1914.

90. Singer, H. D., and Pollock, L. J.: The Histopathology of the Nervous System in Pellagra, Arch. Int. Med. **11**:565 (June) 1913.

91. Smith, J. H.: Pellagroid Skin Lesions in a Case of Cachexia Strumipriva, Tr. Am. Clim. & Clin. A. **45**:15, 1929.

92. Stewart, H. E.: Physiotherapy, New York, Paul B. Hoeber, Inc., 1925.

93. Sullivan, M. X.: Studies in the Biochemistry of Sulphur: II. Further Studies on the Distinctive Reaction for Cysteine and Cystine, Pub. Health Rep. **44**:1421, 1929.

94. Sullivan, M. X., and Dawson, P. R.: Sulfocyanate in Pellagra, J. Biol. Chem. **45**:473, 1921.

95. Sullivan, M. X., and Dawson, P. R.: Phenols in the Urine in Pellagra, Arch. Int. Med. **28**:166 (Aug.) 1921.

96. Sullivan, M. X., and Stanton, R. E.: The Alkali Reserve in Pellagra, Arch. Int. Med. **26**:41 (July) 1920.

97. Sullivan, M. X.; Stanton, R. E., and Dawson, P. R.: Metabolism in Pellagra: A Study of the Urine, Arch. Int. Med. **27**:387 (April) 1921.

98. Sundstroem, E. S.: The Physiological Effects of Tropical Climate, Physiol. Rev. **7**:320, 1927.

99. Thatcher, H. S.: The Outbreak of Pellagra in Arkansas in 1927, J. Arkansas M. Soc. **24**:193, 1928.

100. Throne, B., and Myers, C. N.: Psoriasis: Preliminary Report on Blood Chemistry Studies and Indications for Treatment as Shown by These Findings, New York State J. Med. **28**:914, 1928.

101. Tisdall, F. F., and Brown, A.: Relation of the Altitude of the Sun to Its Antirachitic Effect, J. A. M. A. **92**:860 (March 16) 1929.

102. Li, Tsi-Tung: Quart. Rev. Biol. **4**:401, 1929.

103. United States Census, 14, Mississippi State Compendium.

104. United States Census, 14, South Carolina State Compendium.

105. United States Department of Agriculture, Bureau of Agricultural Economics: Lower Mississippi River Flood, May-July, 1927.

106. United States Department of Agriculture, Weather Bureau: Annual Report, 1914.

107. United States Department of Agriculture, Weather Bureau: Bull. W.

108. United States Department of Agriculture: Yearbook of Agriculture, 1924 and 1930.

109. United States Public Health Reports.

110. Vance, R. B.: Human Factors in Cotton Culture, Chapel Hill, University of North Carolina Press, 1929.

111. Vedder, E. B.: Dietary Deficiency as the Etiological Factor in Pellagra, Arch. Int. Med. **18**:137 (Aug.) 1916.

112. Voegtlin, C.: Recent Work on Pellagra, Pub. Health Rep. **35**:1435, 1920.

113. Voegtlin, C., and Thompson, J. W.: Glutathione Content of Tumor Animals, J. Biol. Chem. **70**:801, 1926.

114. Ward, F. W.: Biochem. J. **17**:898, 1923.

115. Warren, S. L.: The Physiological Effects of Roentgen Radiation upon Normal Body Tissues, Physiol. Rev. **8**:92, 1928.

116. Wells, H. G.: Chemical Pathology, ed. 2, Philadelphia, W. B. Saunders Company, 1914, p. 557.

117. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med. **38**:736 (Dec.) 1926.

118. Wilson, H. E. C.: XIII. Studies in Nitrogen and Sulphur Metabolism, Biochem. J. **20**:76, 1926.

119. Wilson, W. H.: The Pellagra Outbreak in Egypt, Lancet **2**:719, 1920.

120. Wood, E. J.: Pellagra, revised by F. R. Taylor, Oxford Loose Leaf System, London, Oxford University Press, p. 349.

121. Zuntz, N.: Deutsche landwirtsch. Presse, 1919, vol. 29; Jahresb. Thierchem. **49**:594, 1919.

122. Zuntz, N.: Deutsche med. Wchnschr. **46**:145, 1920.

THE ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and as a medium of publication for research and observation in the domain of internal medicine.

Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to Dr. Joseph L. Miller, Editor-in-Chief, 122 South Michigan Boulevard, Chicago, or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, ARCHIVES OF INTERNAL MEDICINE, American Medical Association, 535 North Dearborn Street, Chicago.

Articles are accepted for publication on condition that they are contributed solely to the ARCHIVES OF INTERNAL MEDICINE. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones of illustrations will be supplied by the Association when the original illustrations warrant.

Footnotes and bibliographies should conform to the style of the Quarterly Cumulative Index Medicus, published by the American Medical Association. This requires, in order given: name of author, title of article, name of periodical, with volume, page, month—day of month if weekly—and year. A complete list of abbreviations for standard periodicals, together with a full discussion of the style of the A. M. A. publications, appears in The Art and Practice of Medical Writing, a comprehensive book on the preparation of medical manuscripts, published by the American Medical Association. Price, $1.50.

Matter appearing in the ARCHIVES OF INTERNAL MEDICINE is covered by copyright but, as a rule, no objection will be made to its reproduction in reputable medical journals, if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the ARCHIVES OF INTERNAL MEDICINE, or in any of the other publications issued by the Association, will not be permitted.

Authors will receive one hundred reprints free; additional reprints may be obtained at cost.

The ARCHIVES OF INTERNAL MEDICINE is published monthly. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75, including postage. Single copies, 75 cents, postpaid.

Checks, etc., should be made payable to the AMERICAN MEDICAL ASSOCIATION.

OTHER PERIODICAL PUBLICATIONS
of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (two volumes): Domestic, $7.00; Canadian, $8.50; foreign, $8.50. Single copies, 25 cents.

AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. It includes carefully prepared collective abstracts based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75. Single copies, 75 cents.

ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, society transactions, etc. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75. Single copies, 75 cents.

ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions and full abstracts of the literature on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): Domestic, $5.00; Canadian, $5.40; foreign, $5.75. Single copies, 75 cents.

ARCHIVES OF SURGERY—Monthly. Devoted largely to the investigative and clinical phases of surgery, with monthly reviews on orthopedic and urologic surgery. Well illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original contributions in the field of pathology, with abstracts from foreign and domestic literature, book reviews, the transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): Domestic, $6.00; Canadian, $6.40; foreign, $6.75. Single copies, 75 cents.

QUARTERLY CUMULATIVE INDEX MEDICUS—Quarterly. A complete subject and author index to the worth-while current medical literature of the world. Issued four times a year. Second and fourth volumes bound for permanent reference. Subscription price, calendar year: Domestic, $12.00; Canadian, $12.50; foreign, $12.75.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn St. CHICAGO

CONTENTS

PAGE

THE INFLUENCE OF SOLAR RAYS ON METABOLISM, WITH SPECIAL REFERENCE TO SULPHUR AND TO PELLAGRA IN SOUTHERN UNITED STATES. JAMES H. SMITH, M.D., RICHMOND, VA.. 907